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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> C07D 213/75, 239/58, 215/38 C07D 409/12, 333/62, 333/54 C07C 275/28, A61K 31/44	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 93/24458</b>  <b>(43) International Publication Date:</b> 9 December 1993 (09.12.93)
<b>(21) International Application Number:</b> PCT/US93/03539 <b>(22) International Filing Date:</b> 20 April 1993 (20.04.93)  <b>(30) Priority data:</b> 07/890,050 28 May 1992 (28.05.92) US  <b>(60) Parent Application or Grant</b> (63) Related by Continuation US 07/890,050 (CIP) Filed on 28 May 1992 (28.05.92)  <b>(71) Applicant (for all designated States except US):</b> PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).		<b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> HAMANAKA, Ernest, S. [US/US]; 40 Eagle Ridge Drive, Gales Ferry, CT 06335 (US).  <b>(74) Agents:</b> RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).  <b>(81) Designated States:</b> AU, BG, BR, CA, CZ, DE, JP, KR, NO, NZ, RO, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> NEW <i>N</i> -ARYL AND <i>N</i> -HETEROARYLUREA DERIVATIVES AS INHIBITORS OF ACYL COENZYME A:CHOLESTEROL ACYL TRANSFERASE (ACAT)		
<div style="text-align: center;"> <math display="block">  \begin{array}{c}  \text{Q} \\     \\  \text{R}^1 - \text{N} - \text{C} - \text{NR}^{17}\text{R}^{18} \\    \\  \text{H}  \end{array}  \quad (\text{I})  </math> </div>		
<b>(57) Abstract</b>  A compound of formula (I), the pharmaceutically acceptable salts thereof, wherein Q, R <sup>17</sup> , R <sup>18</sup> and R <sup>1</sup> are as defined below. The compounds of formula (I) are inhibitors of acyl coenzyme A: cholesterol acyltransferase (ACAT) and are useful as hypolipidemic and antiatherosclerosis agents.		

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NEW N-ARYL AND N-HETEROARYLUREA  
DERIVATIVES AS INHIBITORS OF ACYL  
COENZYME A: CHOLESTEROL ACYL TRANSFERASE (ACAT)

Background of the Invention

The present invention relates to new N-aryl and N-heteroarylurea derivatives,  
10 pharmaceutical compositions comprising such compounds, and the use of such  
compounds to inhibit intestinal absorption of cholesterol, lower serum cholesterol and  
reverse the development of atherosclerosis. The compounds are inhibitors of acyl  
coenzyme A: cholesterol acyltransferase (ACAT).

Cholesterol that is consumed in the diet (dietary cholesterol) is absorbed as free  
15 cholesterol by the mucosal cells of the small intestine. It is then esterified by the  
enzyme ACAT, packaged into particles known as chylomicrons, and released into the  
bloodstream. Chylomicrons are particles into which dietary cholesterol is packaged  
and transported in the bloodstream. By inhibiting the action of ACAT, the compounds  
of this invention prevent intestinal absorption of dietary cholesterol and thus lower  
20 serum cholesterol levels. They are therefore useful in preventing atherosclerosis, heart  
attacks and strokes.

By inhibiting the action of ACAT, the compounds of the present invention also  
enable cholesterol to be removed from the walls of blood vessels. This activity renders  
such compounds useful in slowing or reversing the development of atherosclerosis as  
25 well as in preventing heart attacks and strokes.

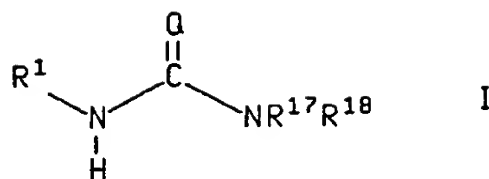
Other inhibitors of ACAT are referred to in United States Patents 4,994,465,  
4,716,175 and 4,743,605 (a divisional of the '175 patent) and in the European Patent  
Applications having publication numbers 0 242 610, 0 245 687, 0 252 524, 0 293 880,  
0 297 610, 0 335 374, 0 335 375, 0 386 487, 0 399 422, 0 415 123, 0 421 456 and  
30 0 439 059. Additional ACAT inhibitors are described in PCT publications WO 90/15048  
and WO 91/04027. Certain ureas and thioureas as antiatherosclerosis agents are  
referred to in United States Patent 4,623,662.

Summary of the Invention

The present invention relates to compounds of the formula

35

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5

wherein Q is oxygen or sulfur

$\text{R}^{17}$  is  $-(\text{CH}_2)_n-(\text{CR}^{19}\text{R}^{20})_z(\text{CH}_2)_r-\text{Ar}$  XXXVIII

wherein n is 0 or an integer from 1 to 3;

z is 0 or 1;

10

and r is 0 or an integer from 1 to 4;

$\text{R}^{19}$  and  $\text{R}^{20}$  are independently selected from hydrogen, optionally halogenated  $(\text{C}_1-\text{C}_{12})$  alkyl, optionally substituted aryl- $(\text{C}_1-\text{C}_6)$  alkyl,  $(\text{C}_3-\text{C}_8)$  cycloalkyl- $(\text{C}_1-\text{C}_5)$  alkyl and Ar; or  $\text{R}^{19}$  and  $\text{R}^{20}$  and the carbon to which they are attached form a  $(\text{C}_4-\text{C}_7)$  cycloalkyl ring or a benzene-fused  $(\text{C}_5-\text{C}_7)$  cyclo-alkyl or -heteroalkyl ring; with the proviso that  $\text{R}^{19}$

15

and  $\text{R}^{20}$  cannot both be hydrogen;

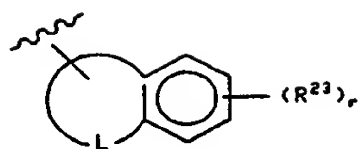
Ar is selected from the group consisting of

20

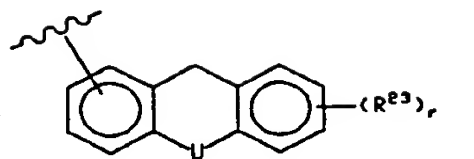
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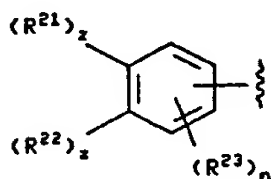
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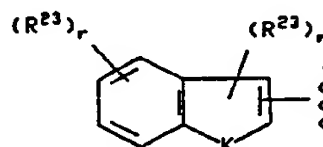
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XXXI



XXXII

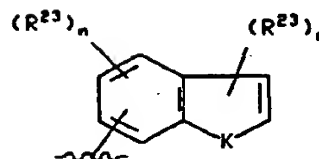


XXXIII



XXXIV

and



XXXV

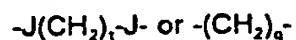
wherein U is J, a direct bond  $-\text{CH}=\text{CH}-$  or  $-\text{CH}_2\text{CH}_2-$ ;

z, n and r are as defined above; x is an integer from 3 to 10 and w is 0 or an integer from 1 to x-1.

25  $\text{R}^{21}$ ,  $\text{R}^{22}$  and each  $\text{R}^{23}$  is independently selected from the group consisting of optionally halogenated  $(\text{C}_1-\text{C}_6)$ alkyl, optionally halogenated  $(\text{C}_1-\text{C}_6)$ alkoxy, optionally halogenated  $(\text{C}_1-\text{C}_6)$ alkylthio, phenyl and halogen; wherein the alkyl groups in said alkyl, alkoxy and alkylthio groups may be straight chained or if comprising three or more carbons may be branched, cyclic or a combination of cyclic and branched or

30 straight chained moieties;

or  $\text{R}^{21}$  and  $\text{R}^{22}$  together form a group of the formula



wherein J is oxygen or sulfur;

t is an integer from 1 to 3;

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and q is an integer from 3 to 5;

K is J- or  $-\text{CH}=\text{CH}-$ ;

L is  $-(\text{CH}_2)_u$  or  $-(\text{CH}_2)_v\text{J}-$ ;

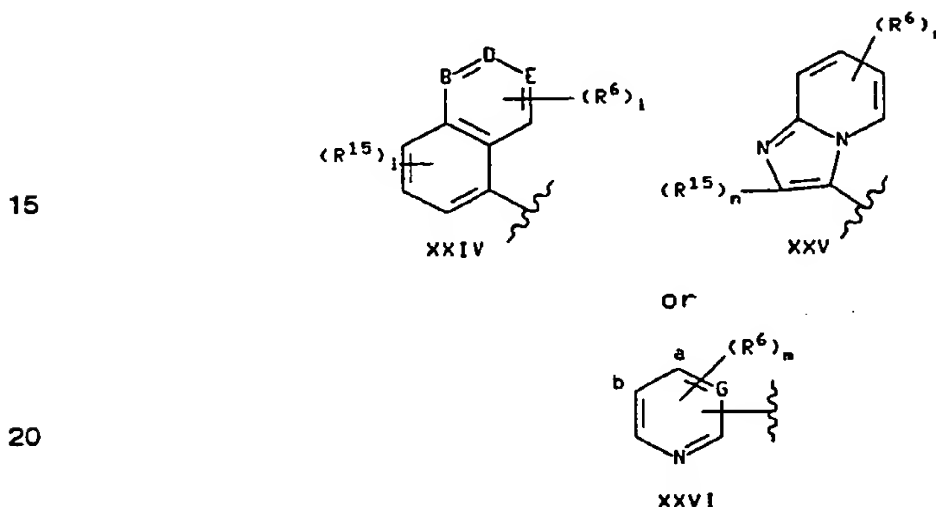
wherein J is as defined above;

5 u is an integer 3 to 5;

and v is 3 or 4;

$\text{R}^{18}$  is hydrogen, optionally substituted  $(\text{C}_1-\text{C}_8)$ alkyl, optionally substituted  $(\text{C}_3-\text{C}_8)$ cycloalkyl, aryl or optionally substituted aryl- $(\text{C}_1-\text{C}_4)$ alkyl with the proviso that  $\text{R}^{18}$  is hydrogen if any one of n, z or r in formula XXXVIII is not 0;

10  $\text{R}^1$  is selected from the group consisting of



wherein m is as defined above;

n is 0 or 1.

25 Each l is independently selected from 0 to 3;

Each  $\text{R}^6$  and  $\text{R}^{15}$  is independently selected from the group consisting of halogen,  $(\text{C}_1-\text{C}_6)$ alkyl,  $(\text{C}_1-\text{C}_6)$  haloalkyl, optionally halogenated  $(\text{C}_1-\text{C}_6)$  alkoxy, optionally halogenated  $(\text{C}_1-\text{C}_6)$  alkylthio,  $(\text{C}_5-\text{C}_7)$  cycloalkylthio, phenyl  $(\text{C}_1-\text{C}_6)$ alkylthio, substituted phenylthio, heteroarylthio, heteroaryloxy,  $(\text{C}_1-\text{C}_6)$  alkylsulfinyl,  $(\text{C}_1-\text{C}_6)$  alkylsulfonyl,  $(\text{C}_5-\text{C}_7)$  cycloalkylsulfinyl,  $(\text{C}_5-\text{C}_7)$  cycloalkylsulfonyl, phenyl  $(\text{C}_1-\text{C}_6)$  alkylsulfinyl, phenyl  $(\text{C}_1-\text{C}_6)$  alkylsulfonyl, substituted phenylsulfinyl, substituted phenylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, and  $\text{NR}^{10}\text{R}^{11}$ , wherein  $\text{R}^{10}$  and  $\text{R}^{11}$  are the same or different and are selected from the group consisting of hydrogen,  $(\text{C}_1-\text{C}_6)$  alkyl, phenyl, substituted phenyl,  $(\text{C}_1-\text{C}_6)$  acyl, aroyl, and substituted aroyl, wherein said substituted phenyl and

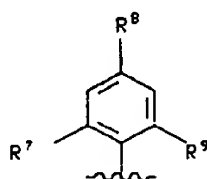
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substituted aroyl groups are substituted with one or more substituents independently selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>1</sub>-C<sub>6</sub>) alkoxy, (C<sub>1</sub>-C<sub>6</sub>) alkylthio, halogen and trifluoromethyl, or R<sup>10</sup> and R<sup>11</sup>, together with the nitrogen to which they are attached, form a piperidine, pyrrolidine or morpholine ring; and

- 5 B, D, E and G are selected from the group consisting of nitrogen and carbon, with the proviso that one or more of B, D and E is nitrogen, and with the proviso that when G is nitrogen, the group XVI is attached to the nitrogen of formula I at the 4 or 5 position of the pyrimidine ring (designated by a and b) wherein any of said nitrogens may be oxidized;

10

or R<sup>1</sup> is

XXVII

- wherein R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> may be the same or different and each is independently selected from the group consisting of optionally halogenated (C<sub>1</sub>-C<sub>5</sub>)alkoxy, optionally halogenated (C<sub>1</sub>-C<sub>5</sub>)alkylthio, optionally halogenated (C<sub>1</sub>-C<sub>5</sub>)alkyl and halogen; with the proviso that when R<sup>1</sup> is a group of the formula XXVII Ar is a group of formula XXXII, XXXIII or XXXV and when Ar is XXXII R<sup>19</sup> or R<sup>20</sup> is not alkyl and r in formula XXXVIII is 0; or a pharmaceutically acceptable salt of said compound.
- 15

Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

- Unless otherwise indicated, the term "alkyl", as used herein, may be straight, branched or cyclic, and may include straight and cyclic moieties as well as branched and cyclic moieties.
- 20

Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

- 25 The term "one or more carbons of said non-aromatic ring", as used herein, refers to from one to all of the carbon atoms that are part of the non-aromatic ring of any of



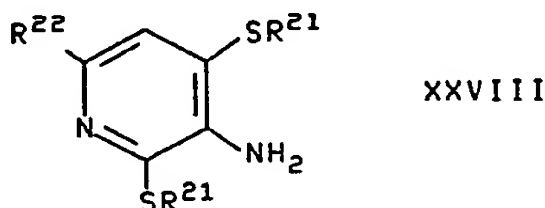
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the aryl-fused or heteroaryl-fused systems described above, and not part of the aromatic ring of said aryl-fused system.

The term "one or more carbons of said aromatic ring", as used herein, refers to from one to all of the carbon atoms that are part of the aromatic ring of any of the  
 5 aryl-fused and heteroaryl-fused systems described above, or are part of both said aromatic and non-aromatic rings of said aryl-fused and heteroaryl-fused system.

The compounds of formula I may have optical centers and therefore may occur in different stereoisomeric configurations. The invention includes all stereoisomers of such compounds of formula I, including mixtures thereof.

10 The present invention also relates to compounds of the formula



15

wherein  $R^{21}$  is  $(C_1-C_3)$  alkyl and  $R^{22}$  is hydrogen or  $(C_1-C_3)$ -alkyl.

Preferred compounds of formula I are those wherein  $R^1$  is 2,4,6-trifluorophenyl, 2,6-diisopropylphenyl, 2,4-difluorophenyl, 6-methoxyquinolin-5-yl, 6-methylquinolin-  
 20 5-yl, 6-methylthioquinolin-5-yl, 6-methoxyisoquinolin-5-yl, 6-methylthioisoquinolin-5-yl, 6-methylthio-8-acetaminoquinolin-5-yl, 4,6-bis(methylthio)pyrimidin-5-yl, 4,6-bis(methylthio)-2-methylpyrimidin-5-yl, 2,4-bis(methylthio)pyridin-3-yl, 2,4-bis(methylthio)-6-methylpyridin-3-yl, 2,4-bis(ethylthio)-6-methylpyridin-3-yl, 2,4-bis(methylthio)pyridin-3-yl and 2,4-bis(isopropylthio)-6-methylpyridin-3-yl.

25 Specific preferred compounds of formula I are:

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(4-isopropylbenzyl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2,5-dimethylbenzyl)-N'-(indan-2-yl)urea;

30 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2,4-dimethylbenzyl)-N'-(indan-2-yl)urea;

N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(indan-2-yl)-N'-(4-isopropylbenzyl)urea;

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- N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(2,4-dimethylbenzyl)-N'-(indan-2-yl)urea;
- N-(2,5-Dimethylbenzyl)-N-(indan-2-yl)-N'-(6-methylthioquinolin-5-yl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2-chlorobenzyl)-N'-(indan-2-yl)urea;
- 5 N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(2,5-dimethylbenzyl)-N'-(indan-2-yl)urea;
- N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(indan-2-yl)-N'-[4-(3-methylbutyl)benzyl]urea;
- 10 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-[4-(3-methylbutyl)benzyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(naphth-1-ylmethyl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(naphth-2-ylmethyl)urea;
- 15 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(4-t-butylbenzyl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(4-phenylbenzyl)urea;
- 20 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(naphth-1-ylmethyl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(naphth-2-ylmethyl)urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(4-phenylbenzyl)urea;
- 25 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(fluoren-2-ylmethyl)urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(naphth-2-ylmethyl)urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-heptyl-N'-[naphth-2-ylmethyl]urea;
- 30 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-heptyl-N'-(2,4,6-trimethylbenzyl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(4-phenylbenzyl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(fluoren-2-ylmethyl)urea;

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N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(4-isopropylbenzyl)-N'-(1,2,3,4-tetrahydro-naphth-2-yl)urea;

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-heptyl-N'-(3-methylbenzo[b]thiophen-2-ylmethyl)urea;

5 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(1,2,3,4-tetrahydronaphth-2-yl)-N'-(2,4,6-trimethylbenzyl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(naphth-2-ylmethyl)urea;

10 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(4-isopropylbenzyl)urea;

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(2,4-dimethylbenzyl)-N'-(indan-2-yl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(4-isopropylbenzyl)-N'-(6,7,8,9-tetrahydro-5H-benzocyclohepten-7-yl)urea;

15 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(2,4,6-trimethylbenzyl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(2,4,6-trimethylbenzyl)urea;

20 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2,3-dichlorobenzyl)-N'-(indan-2-yl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2,2-diphenylethyl]urea;

N-(2,2-Diphenylethyl)-N'-(6-methylthioquinolin-5-yl)urea;

N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(2,2-diphenylethyl)urea;

N-[4,6-Bis(methylthio)pyrimidin-5-yl]-N'-(2,2-diphenylethyl)urea;

25 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(1-phenylcyclopentyl)methyl]urea;

N-(6-Methylthioquinolin-5-yl)-N'-[(1-phenylcyclopentyl)methyl]urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[{1-(4-methylphenyl)cyclopentyl}methyl]urea;

N-[{1-(4-Methylphenyl)cyclopentyl}methyl]-N'-(6-methylthioquinolin-5-yl)urea;

30 N-(6-Methylthioquinolin-5-yl)-N'-[(1-phenylcyclohexyl)methyl]urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(1-phenylcyclohexyl)methyl]urea;

N-[{1-(4-Methylphenyl)cyclohexyl}methyl]-N'-(6-methylthioquinolin-5-yl)urea;

N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-[{1-(4-methylphenyl)cyclohexyl}methyl]urea;

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- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[1-(4-methylphenyl)cyclohexyl]methyl]urea;
- N-2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-ethyl-2-phenyl)butyl]urea;
- N-[2,4-Bis(isopropylthio)-6-methylpyridin-3-yl]-N'-[(2-ethyl-2-phenyl)butyl]urea;
- 5 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-ethyl-2-{2-methylphenyl})butyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-phenyl-2-propyl)pentyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2-methylphenyl}-2-propyl)pentyl]urea;
- 10 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2-methylphenyl}-2-butyl)hexyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,5-dimethoxyphenyl}-2-propyl)pentyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,3-dimethoxyphenyl}-2-propyl)pentyl]urea;
- 15 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,5-dimethylphenyl}-2-propyl)pentyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2-methylphenyl)hexyl]urea;
- N-[2-(2-Methylphenyl)hexyl]-N'-[6-methylthioquinolin-5-yl]urea;
- 20 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(4-methylphenyl)heptyl]urea;
- N-[2-(4-Methylphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3-methylphenyl)heptyl]urea;
- N-[2-(3-Methylphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;
- N-[2-(3-Methylphenyl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea;
- 25 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)hexyl]urea;
- N-[2-(2,5-Dimethylphenyl)hexyl]-N'-(6-methylthioquinolin-5-yl)urea;
- N-[2-(2,5-Dimethylphenyl)hexyl]-N'-(6-methoxyquinolin-5-yl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)heptyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,4-dimethylphenyl)hexyl]urea;
- 30 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3-methylphenyl)hexyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,4-dimethylphenyl)heptyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)heptyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-2-yl)hexyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)hexyl]urea;

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- N-(6-Methylthioquinolin-5-yl)-N'-[2-(naphth-1-yl)hexyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,3-dimethoxyphenyl)heptyl]-  
 urea;
- 5 N-[2-(2,3-Dimethoxyphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3-methylphenyl)octyl]urea;  
 N-[2-(3-Methylphenyl)octyl]-N'-(6-methoxyquinolin-5-yl)urea;  
 N-[2-(3-Methylphenyl)octyl]-N'-(6-methylthioquinolin-5-yl)urea;  
 N-[2-(Naphth-1-yl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea;  
 N-[2-(Naphth-1-yl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;
- 10 N-[2-(2,4-Dimethylphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;  
 N-[2-(2,4-Dimethylphenyl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3,4,5-  
 trimethoxyphenyl)heptyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethyl-4-  
 15 methoxyphenyl)heptyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethoxyphenyl)-  
 phenylbutyl]urea;  
 N-[2-(2,5-Dimethoxyphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;  
 N-[2-(2,5-Dimethoxyphenyl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea;
- 20 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-  
 dimethoxyphenyl)heptyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethoxyphenyl)octyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-2-[2-(3-methylphenyl)-6,6,6-  
 25 trifluorohexyl]urea;  
 N-[2-(3-Methylphenyl)heptyl]-N'-(6-pentylthioquinolin-5-yl)urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(5-chlorobenzo[b]thiophen-3-  
 yl)heptyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-dimethylphenyl)heptyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)octyl]urea;
- 30 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-2-{3-  
 methylphenyl}hexyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,5-dimethylphenyl}-4-  
 phenylbutyl]urea;

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- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-5-phenylpentyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)-6-methylheptyl]urea;
- 5 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)-6-methylheptyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-6-methylheptyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)heptyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-6-phenylhexyl]urea;
- 10 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)heptyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,4,6-trimethylphenyl)octyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-6,6,6-trifluorohexyl]urea;
- 15 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(5-methylbenzo[b]thiophen-3-yl)heptyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2-chlorobenzo[b]thiophen-3-yl)heptyl]urea;
- N-[2-(2,5-Dimethylphenyl)heptyl]-N'-[6-methylthioquinolin-5-yl]urea;
- 20 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-6-methylheptyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-5-phenylpentyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)octyl]urea;
- 25 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-5-methylhexyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2-chlorobenzo[b]thiophen-3-yl)-6-methylheptyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2-chlorobenzo[b]thiophen-3-yl)-5-methylhexyl]urea;
- 30 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(5,6,7,8-tetrahydronaphth-1-yl)heptyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-dimethylphenyl)heptyl]urea;

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- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2-chlorobenzo[b]thiophen-3-yl)heptyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-dimethylphenyl)octyl]urea;
- N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethyl-4-methoxyphenyl)heptyl]urea;
- 5 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(5-methylbenzo[b]thiophen-3-yl)heptyl]urea;
- N-[2-(2-Chlorobenzo[b]thiophen-3-yl)-5-methylhexyl]-N'-(2,6-diisopropyl)urea;
- N-(2,6-Diisopropylphenyl)-N'-[2-(5-methylbenzo[b]thiophen-3-yl)-5-methylhexyl]urea;
- 10 N-[2-(Benzo[b]thiophen-3-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea;
- N-[2-(Benzo[b]thiophen-3-yl)-6-methylheptyl]-N'-(2,6-diisopropylphenyl)urea;
- N-[2-(2-Chlorobenzo[b]thiophen-3-yl)-6-methylheptyl]-N'-(2,6-diisopropylphenyl)urea;
- 15 N-(2,6-Diisopropylphenyl)-N'-[2-(5-methylbenzo[b]thiophen-3-yl)-6,6,6-trifluorohexyl]urea;
- N-[2-(2-Chlorobenzo[b]thiophen-3-yl)-6,6,6-trifluorohexyl]-N'-(2,6-diisopropylphenyl)urea;
- N-(2,6-Diisopropylphenyl)-N'-[2-(naphth-2-yl)-6,6,6-trifluorohexyl]urea;
- 20 N-[7,7-Difluoro-2-(naphth-1-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea;
- N-[7,7-difluoro-2-(2-chlorobenzo[b]thiophen-3-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea;
- N-[2-(5-Chlorobenzo[b]thiophen-3-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea;
- N-[2-(2-Chlorobenzo[b]thiophen-3-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea;
- 25 N-[2-(5-Chlorobenzo[b]thiophen-3-yl)-6,6,6-trifluorohexyl]-N'-(2,6-diisopropylphenyl)urea;
- N-(2,6-(Diisopropylphenyl)-N'-[2-(5-methylbenzo[b]thiophen-3-yl)heptyl]urea;
- N-[2-(5-Chlorobenzo[b]thiophen-3-yl)-6-methylheptyl]-N'-(2,6-diisopropylphenyl)urea;
- 30 N-(2,6-(Diisopropylphenyl)-N'-[2-(2,5-dimethylphenyl)-6,6,6-trifluorohexyl]urea;
- N-[7,7-Difluoro-2-(2,5-dimethylphenyl)heptyl]-N'-(2,6-diisopropylphenyl)urea;
- N-(2,6-Diisopropylphenyl)-N'-[2-(naphth-1-yl)heptyl]urea;
- and N-(2,6-Diisopropylphenyl)-N'-[6-methyl-2-(naphth-1-yl)heptyl]urea.

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The present invention also relates to all radiolabelled forms of the compounds of the formulae I, II and XXVIII. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays in both animals and man.

5

The present invention also relates to a pharmaceutical composition for inhibiting ACAT, inhibiting intestinal absorption of cholesterol, reversing or slowing the development of atherosclerosis, or lowering the concentration of serum cholesterol in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in inhibiting ACAT, inhibiting intestinal absorption of cholesterol, reversing or slowing the development of atherosclerosis, or lowering the concentration of serum cholesterol, and a pharmaceutically acceptable carrier.

15       The present invention also relates to a method for inhibiting ACAT, inhibiting intestinal absorption of cholesterol, reversing or slowing the development of atherosclerosis, or lowering the concentration of serum cholesterol in a mammal, including a human, comprising administering to a mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in inhibiting  
20 ACAT, inhibiting intestinal absorption of cholesterol, reversing or slowing the development of atherosclerosis, or lowering the concentration of serum cholesterol.

Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I salts are the salts of hydrochloric acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid,  
25 methanesulfonic acid, tartaric acid, di-p-toluoyl tartaric acid, and mandelic acid.

#### Detailed Description of the Invention

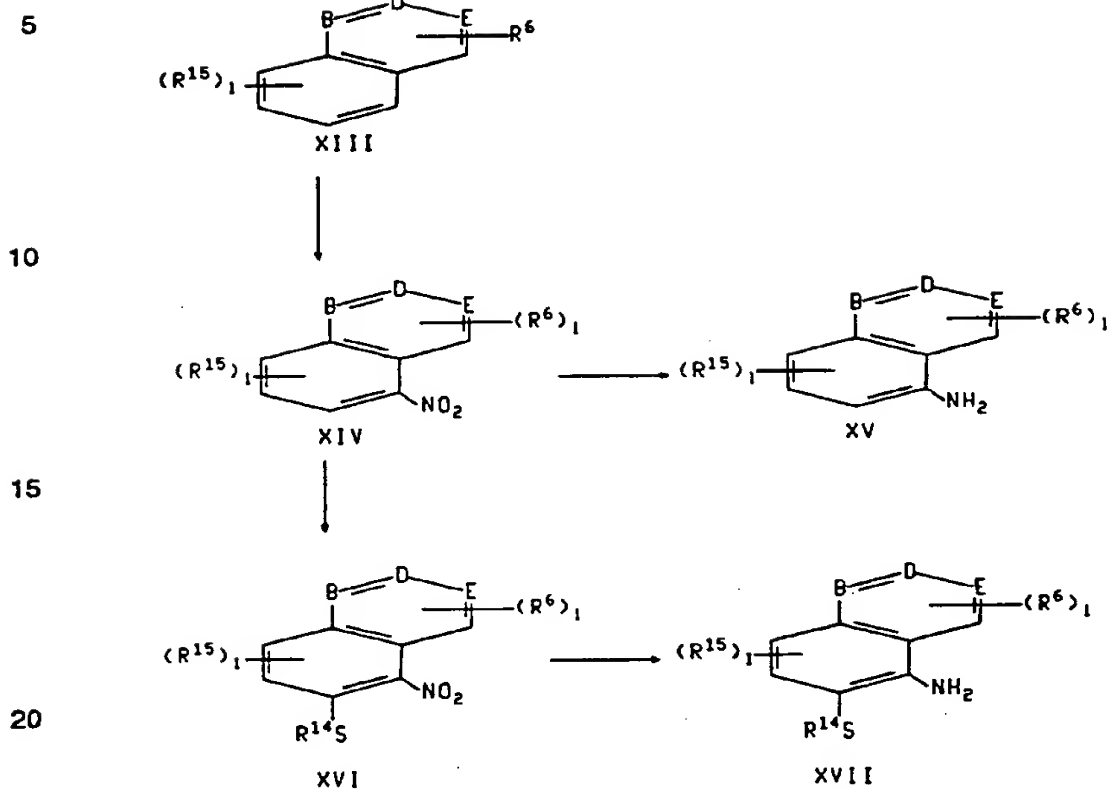
The reaction scheme below illustrates the synthesis of certain 5-aminoquinolines and 5-aminoisoquinolines used in the practice of this invention.

Except where otherwise stated, Q, R<sup>1</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, n, m, o, p,  
30 A, B, D, E and G in the reaction schemes and discussion that follows are defined as above.



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## SCHEME 1



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The aminopyrimidine and aminopyridine intermediates used in the present invention are known in the literature or may be prepared by methods known in the art from intermediates that are known in the literature or commercially available. References for the preparation of many of the pyrimidine and pyridine intermediates can be found  
5 in the monographs "The Pyrimidines", ed. by D.J. Brown (1962) and "Pyridine and its Derivatives", ed. by R.A. Abramovitch (1961), Interscience Publishers, Inc., New York, N.Y., and their supplements. The preparation of certain of these intermediates is described in greater detail below.

2,6-Disubstituted-5-amino-pyrimidine derivatives may be prepared by reacting  
10 the appropriately substituted 4,6-dihydroxypyrimidine with a nitrating agent such as fuming nitric acid in acetic acid at a temperature from about 15°C to about 40°C for a period of about 1 to about 5 hours. The resulting 5-nitropyrimidines are converted to the 2,4-dichloro-5-nitropyrimidine intermediates using a chlorinating agent such as phosphoryl chloride, alone or in the presence of a base, preferably diethylaniline, at a  
15 temperature from about 100 to about 115°C for a period of about 0.5 to about 2 hours. Procedures for carrying out these transformations are described in J. Chem. Soc., 3832 (1954).

The 2,6-bis(alkylthio)-5-nitropyrimidine derivatives may be prepared by reacting the appropriate dichloro intermediate with two equivalents of sodium alkylthiolate in a  
20 solvent such as dimethylformamide or, preferably, methanol, for about 4 to about 16 hours at a temperature from about 0 to about 30°C, preferably at ambient temperature. Monosubstitution of the dichloro intermediate is accomplished by using one equivalent of nucleophile, at a reaction temperature of about 0 to about 100°C, depending on the reactivity of the nucleophile, in an inert solvent such as dimethyl-formamide or  
25 tetrahydrofuran, for a period of about 4 to about 16 hours.

The resulting monochloro derivative is then reacted with one equivalent of a different nucleophile to yield a disubstituted derivative with different substituents on the carbon atoms at positions 2 and 4. The 2,6-disubstituted-5-nitropyrimidine is reduced  
30 using a reducing agent such as stannous chloride in concentrated hydrochloric acid or hydrogen gas with an appropriate catalyst, to yield the corresponding 5-aminopyrimidine derivative.

The novel pyridines of formula XXVIII and other 2,4-disubstituted-3-aminopyridine derivatives may be prepared by reacting the appropriate 2,4-dihydroxypyridine with a nitrating agent such as concentrated nitric acid at 80-100°C for 15-60 minutes. For

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example, the preparation of 2,4-dihydroxy-6-methyl-3-nitropyridine is described in J. Heterocyclic Chem., 1970, 7, 389. The resulting 2,4-dihydroxy-3-nitro-pyridine is sequentially converted to the 2,4-dichloro-3-nitropyridine, 2,4-disubstituted-3-nitropyridine and 2,4-disubstituted-3-aminopyridine derivatives, using reaction conditions similar to those described above for the pyrimidine series.

The preparation of certain 5-aminoquinolines and 5-aminoisoquinolines is illustrated in scheme 1. Referring to scheme 1, 5-aminoquinolines and isoquinolines of the formulae XV and XVII may be prepared as follows. A quinoline or isoquinoline of the formula XIII is nitrated at the 5 position, respectively, by reacting it with a nitrating agent such as nitric acid or potassium nitrate with or without an acid catalyst such as sulfuric acid, for from about 2 to 16 hours at a temperature from about 0-100°C. The nitro compound of formula XIV so formed is then reduced using a reducing agent such as stannous chloride, iron, zinc, or hydrogen gas with an appropriate catalyst, with or without an acid catalyst such as hydrochloric acid, for from about 2 to 16 hours at a temperature from about 0-100°C, to yield the corresponding 5-aminoquinoline or 5-aminoisoquinoline of formula XV.

Compounds of the formula XVII, wherein  $R^{15}$  is  $-SR^{14}$  and is attached to the quinoline or isoquinoline ring at the 6 position, and wherein  $R^{14}$  is  $(C_1-C_6)$  alkyl,  $(C_5-C_7)$  cycloalkyl, phenyl  $(C_1-C_4)$  alkyl, phenyl, substituted phenyl, heteroaryl, or substituted heteroaryl, may be prepared as follows. A compound of the formula XIV, wherein  $R^5$  is  $-Cl$  and is attached to the quinoline or the isoquinoline ring at the 6 position, is reacted with a compound of the formula  $R^{14}SH$ , wherein  $R^{14}$  is as defined above, and a base such as sodium hydride, or such compound of the formula XIV is reacted with a compound of the formula  $R^{14}SNa$ , wherein  $R^{14}$  is as defined above, in an inert solvent such as tetrahydrofuran, for about 4 to 16 hours at a temperature of from about -10°C to room temperature. The preferred temperature is -10°C. This reaction yields a compound of the formula XVI, which is then converted to the corresponding 5-aminoquinoline or isoquinoline of the formula XVII by the method described above for reduction of compounds of formula XIV.

Treatment of the compound of formula  $R^{17}R^{18}NH$  with a compound of the formula  $R^1N=C=Q$  yields the corresponding urea ( $Q=O$ ) or thiourea ( $Q=S$ ) of the formula I. Procedures for the preparation of compounds of the formula  $R^1N=C=Q$  are known in the literature and several methods are reviewed in "Organic Functional Group Preparations, Vol 1", Chapter 12, Academic Press, New York (1968). The preparation

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of ureas and thioureas by the reaction of amines with isocyanates and isothiocyanates, respectively, are reviewed in Organic Functional Group Preparations, Vol. 2, Chapter 6, Academic Press, New York (1971).

Compounds of the formula  $R^1N=C=O$  may be obtained by reacting compound  
5 of the formula  $R^1NH_2$  with 1 to 6 equivalents of an appropriate reagent such as phosgene, trichloromethyl chloroformate or bis(trichloromethyl)carbonate. The reaction is generally carried out in an inert ether, aromatic hydrocarbon or chlorinated hydrocarbon solvent such as dioxane, diisopropyl ether, benzene, toluene, dichloromethane or chloroform. It may be conducted in the presence of a base such  
10 as a tertiary amine (e.g., pyridine, triethylamine or quinoline). Reaction temperatures may range from about  $0^\circ C$  to about  $120^\circ C$ , and are preferably from about  $20^\circ C$  to about  $100^\circ C$ . Preferably, the heterocyclic amine of formula  $R^1NH_2$  is reacted with 1 to 2 equivalents of trichloromethyl chloroformate in refluxing dichloromethane for about 18 hours.

15 The reaction of compounds of the formula  $R^1N=C=Q$  with compounds of formula  $R^{17}R^{18}NH$  to form compounds of the formula I is carried out in an inert, anhydrous solvent such as chloroform, benzene, dimethylformamide, dioxane or tetrahydrofuran, at a temperature from about  $20^\circ C$  to  $100^\circ C$ , for about 3 to 30 hours, preferably in dimethylformamide at about  $80^\circ C$  for about 16 hours.

20 Amines of the formula  $NHR^{17}R^{18}$  may be prepared by a variety of methods well known in the art (see e.g., Vogel's Textbook of Practical Organic Chemistry, Longman, Inc., New York, pp. 769-782 and pp. 717-718 (5th ed. 1989), Organic Functional Group Preparations, Vol 2. Academic Press, New York, pp. 401-405 (2nd ed. 1983). Other examples of methods for the preparation of amines of the formula  $NHR^{17}R^{18}$  are  
25 described in EP 0399 422 A1, EP 0415 123 A2 and EP 0439 059 A2.

For instance, compounds of the formula  $R^{17}R^{18}NH$  wherein  $R^{19}$  is hydrogen and  $R^{20}$  is optionally substituted aryl-( $C_1$ - $C_6$ )alkyl or optionally halogenated ( $C_1$ - $C_{12}$ ) alkyl may be prepared by treating a compound of the formula  $Ar-CH_2-CN$  with an alkali metal amide followed by addition of a compound of the formula  $R^{20}I$  to form a compound of  
30

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$\text{R}^{20}$   
|  
the formula  $\text{Ar}-\text{CH}-\text{CN}$  which is subsequently reduced to the amine of the formula

5

$\text{R}^{20}$   
|  
 $\text{Ar}-\text{CH}-\text{CH}_2-\text{NH}_2$  by standard means.

The alkali metal moieties of the amides may be exemplified by lithium, sodium  
10 and potassium, preferably lithium. A most preferred amide is lithium diisopropylamide.

The reduction of the nitriles may be effected using borane, e.g. in the form of its complex with tetrahydrofuran, or by hydrogenation in the presence of Raney nickel.

Except where otherwise noted, pressure is not critical in any of the above reactions. Preferred temperatures for the above reactions were stated where known. In  
15 general, the preferred temperature for each reaction is the lowest temperature at which product will be formed. The preferred temperature for a particular reaction may be determined by monitoring the reaction using thin layer chromatography.

Preparation of certain novel intermediates useful in preparing the compounds of the invention is described in preparative examples A through R.

20 The novel compounds of formula I and the pharmaceutically acceptable salts thereof are useful as inhibitors of acyl coenzyme A: cholesterol acyltransferase (ACAT). As such they inhibit intestinal absorption of cholesterol in mammals and are useful in the treatment of high serum cholesterol in mammals, including humans. As used herein, treatment is meant to include both the prevention and alleviation of high serum  
25 cholesterol. The compound may be administered to a subject in need of treatment by a variety of conventional routes of administration, including orally, parenterally and topically. In general, these compounds will be administered orally or parenterally at dosages between about 0.08 and about 30 mg/kg body weight of the subject to be treated per day, preferably from about .08 to 5 mg/kg. For an adult human of  
30 approximately 70 kg of body weight, the usual dosage would, therefore, be about 5.6 to about 2100 mg per day. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated and the activity of the compound being employed. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

35 A compound of formula I or a pharmaceutically acceptable salt thereof may be administered alone or in combination with pharmaceutically acceptable carriers, in

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either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The resulting pharmaceutical compositions are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of a compound of formula I or a pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. Such solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, the sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The activity of the compounds of the present invention as ACAT inhibitors may be determined by a number of standard biological or pharmacological tests. For example, the following procedure was used to determine the ACAT inhibiting activity of compounds of formula I. ACAT was assayed in microsomes isolated from chow fed Sprague-Dawley rats according to Bilheimer, J.T., Meth. Enzymol., 111, ps 286-293 (1985), with minor modifications. Microsomes from rat liver were prepared by differential centrifugation and washed with assay buffer prior to use. The assay mixture contained 25  $\mu$ l of BSA (40 mg/ml), 30  $\mu$ l of rat liver microsome solution (100  $\mu$ g

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microsomal protein), 20  $\mu$ l of assay buffer (0.1 M  $K_2PO_4$ , 1.0 mM reduced Glutathione, pH 7.4), 20  $\mu$ g of cholesterol in 100  $\mu$ l of a 0.6% Triton WR-1339 solution in assay buffer, and 5  $\mu$ l of test compound dissolved in 100% DMSO (total volume = 180  $\mu$ l). The assay mixture was incubated for 30 min at 37°C. The reaction was started by the addition of 20  $\mu$ l of  $^{14}C$ -Oleoyl-CoA solution (1000  $\mu$ M, 2,000 dpm/nmol) and run for 15 min at 37°C. The reaction was stopped by the addition of 1 ml EtOH. The lipids were extracted into 4 ml hexane. A 3 ml aliquot was dried under  $N_2$ , and resuspended in 100  $\mu$ l of chloroform. 50  $\mu$ l of chloroform were spotted on a heat activated TLC plate and developed in hexane: diethyl ether: acetic acid (85:15:1, v:v:v). Incorporation of radioactivity into cholesteryl esters was quantified on a Berthold LB2842 Linear TLC Analyzer. ACAT inhibition was calculated relative to a DMSO control assay.

The activity of the compounds of formula I in inhibiting intestinal absorption of cholesterol may be determined by the procedure of Melchoir and Harwell, J. Lipid. Res., 26, 306-315 (1985).

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra ( $^1H$  NMR) and  $^{13}C$  nuclear magnetic resonance spectra ( $^{13}C$  NMR) were measured for solutions in deuteriochloroform ( $CDCl_3$ ) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; q, quintet; hx, hextet; h, heptet, m, multiplet; br, broad; vb, very broad; c, complex.

#### PREPARATION OF INTERMEDIATES

##### PREPARATIVE EXAMPLE A

##### 5-Iodo-1,1-difluoropentane

A solution of 5-bromo-1,1-difluoropentane (2.65 g, 14.2 mmol) and sodium iodide (10.63 g, 70.8 mmol) in acetone (150 ml) was refluxed under nitrogen overnight. The reaction mixture was then filtered and the filtrate was concentrated at atmospheric pressure. The residue was dissolved in dichloromethane (50 ml) and the solution was washed with water (2X30 ml) and brine (30 ml), dried (sodium sulfate) and concentrated under reduced pressure at room temperature. The crude product was distilled under reduced pressure to yield the title compound as a yellowish liquid (2.24 g, 93% yield), bp 73-75°C, 10 mm Hg.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  1.59 (m, 2H), 1.84 (c, 4H), 3.2 (t, 2H), 5.63, 5.82, 6.01 (3t, total 1H).

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PREPARATIVE EXAMPLE B2-(2-Chlorobenzo[b]thiophen-3-yl)-7,7-difluoroheptanenitrile

A solution of lithium diisopropylamide in cyclohexane (5.13 mmol, 3.42 ml of a 1.5M solution) was added dropwise to a solution of (2-chlorobenzo[b]thiophen-3-yl)acetonitrile (1.06 g, 5.13 mmol) in tetrahydrofuran (10 ml) cooled to -70°C under nitrogen. The resulting solution was stirred at -70°C for 20 min, then a solution of 5-iodo-1,1-difluoropentane (1.2 g, 5.13 mmol) in tetrahydrofuran (5 ml) was slowly added at -70°C. The reaction mixture was stirred at -70°C for 1 hr, then slowly allowed to warm to room temperature and left at that temperature overnight. Water (60 ml) was added to the reaction solution and the resulting mixture was extracted with ethyl acetate (3X70 ml). The combined ethyl acetate extracts were washed with brine (80 ml), dried (sodium sulfate) and concentrated in vacuo. The crude product (2.1 g) was purified by column chromatography on silica gel (200 g), eluting with 4:1 hexane/dichloromethane followed by 7:3 hexane/dichloromethane to yield the title compound as an oil (950 mg, 59% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.4-1.7 (c, 4H), 1.7-2.05 (c, 3H), 2.2 (c, 1H), 4.3 (t, 1H), 5.6, 5.78, 5.98 (3t, total 1H), 7.42 (m, 2H), 7.75 (d, 1H), 7.95 (d, 1H).

In a similar manner, the following nitriles were synthesized:

PREPARATIVE EXAMPLE C2-(naphth-1-yl)-7,7-difluoroheptanenitrile

75% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.44-1.72 (c, 4H), 1.72-1.94 (c, 2H), 2.07 (m, 2H), 4.57 (t, 1H), 5.6, 5.8, 5.99 (3t, total 1H), 7.44-7.64 (m, 3H), 7.69 (d, 1H), 7.9 (m, 3H).

PREPARATIVE EXAMPLE D2-(2,5-Dimethylphenyl)-6-phenylhexanenitrile

86% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.48-2.0 (c, 6H), 2.28 (s, 3H), 2.34 (s, 3H), 2.63 (t, 2H), 3.89 (q, 1H), 7.06 (m, 2H), 7.12-7.32 (m, 6H)

PREPARATIVE EXAMPLE E2-(2-Chlorobenzo[b]thiophen-3-yl)-7,7-difluoroheptanamine

A solution of borane-tetrahydrofuran complex in tetrahydrofuran (6.07 mmol, 6.07 ml of a 1.0M solution) was added dropwise to a solution of (2-chlorobenzo[b]thiophen-3-yl)-7,7-difluoroheptanenitrile (950 mg, 3.03 mmol) in tetrahydrofuran (15 ml) at room temperature under nitrogen and the reaction was left at room temperature overnight. Aqueous hydrochloric acid (5 ml of a 3N solution) was



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then added and reaction mixture was refluxed for 30 min followed by removal of the tetrahydrofuran in vacuo. The resulting aqueous phase was diluted with water (10 ml) and extracted with ethyl acetate (3X30 ml). The combined ethyl acetate extracts were washed with brine (40 ml), dried (sodium sulfate) and concentrated in vacuo. The  
5 residue (930 mg) was purified by column chromatography on silica gel (100 g) eluting with 9:1 ethyl acetate/methanol to yield the title compound as an oil (632 mg, 66% yield).

In a similar manner, the following amines were synthesized:

PREPARATIVE EXAMPLE F

10 12-(2-Chlorobenzo[b]thiophen-3-yl)-5-methylhexanamine

67% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79, 0.80, 0.81, 0.83 (2d, 6H), 0.92-1.08 (m, 1H), 1.1-1.28 (m, 1H), 1.5 (h, 1H), 1.66 (b, 2H), 1.78 (m, 1H), 1.94 (c, 1H), 3.09 (m, 1H), 3.18-3.37 (c, 2H), 7.32 (c, 2H), 7.71 (c, 1H), 7.79 (c, 1H).

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PREPARATIVE EXAMPLE G

5-Methyl-2-(5-methylbenzo[b]thiophen-3-yl)hexanamine

53% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.84 (d, 6H), 1.18 (c, 2H), 1.52 (h, 1H), 1.75 (bq, 2H), 2.02 (b, 2H), 2.49 (s, 3H), 3.0 (d, 2H), 3.12 (p, 1H), 7.1 (s, 1H), 7.17 (d, 1H), 7.59  
20 (s, 1H), 7.73 (d, 1H).

PREPARATIVE EXAMPLE H

2-(Benzo[b]thiophen-3-yl)heptanamine

65% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 3H), 1.25 (c, 6H), 1.76 (c, 2H), 2.05 (b, 2H),  
25 3.03 (c, 2H), 3.19 (p, 1H), 7.14 (s, 1H), 7.36 (c, 2H), 7.81 (m, 1H), 7.87 (m, 1H).

PREPARATIVE EXAMPLE I

2-(Benzo[b]thiophen-3-yl)-6-methylheptanamine

66% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78, 0.80, 0.81, 0.82 (2d, 6H), 1.1-1.44 (c, 4H),  
30 1.47 (h, 1H), 1.74 (q, 2H), 2.06 (b, 2H), 3.04 (c, 2H), 3.19 (p, 1H), 7.14 (s, 1H), 7.36 (c, 2H), 7.84 (m, 2H).

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PREPARATIVE EXAMPLE J2-(5-Methylbenzo[b]thiophen-3-yl)-6,6,6-trifluorohexanamine

51% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.54 (m, 2H), 1.69 (b, 2H), 1.86 (c, 2H), 2.06 (m, 2H), 2.49 (s, 3H), 3.03 (d, 2H), 3.16 (p, 1H), 7.12 (s, 1H), 7.19 (d, 1H), 7.57 (s, 1H), 7.75 (d, 1H).

PREPARATIVE EXAMPLE K2-(2-Chlorobenzo[b]thiophen-3-yl)-6,6,6-trifluorohexanamine

60% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.35-1.7 (c, 4H), 1.89 (c, 1H), 2.05 (c, 3H), 3.09 (q, 1H), 3.2-3.4 (c, m, 2H), 7.34 (m, 2H), 7.75 (m, 2H).

PREPARATIVE EXAMPLE L2-(2-Chlorobenzo[b]thiophen-3-yl)heptanamine

68% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.2 (c, 6H), 1.65 (b, 2H), 1.78 (c, 1H), 1.95 (c, 1H), 3.07 (q, 1H), 3.16-3.38 (c, m, 2H), 7.32 (c, 2H), 7.72 (m, 1H), 7.8 (m, 1H).

PREPARATIVE EXAMPLE M2-(5-Chlorobenzo[b]thiophen-3-yl)heptanamine

60% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.84 (t, 3H), 1.26 (c, 6H), 1.65-1.9 (c, 4H), 3.0 (d, 2H), 3.1 (p, 1H), 7.19 (s, 1H), 7.29, 7.30, 7.32, 7.33 (q, 1H), 7.77 (m, 2H).

PREPARATIVE EXAMPLE N2-(5-Methylbenzo[b]thiophen-3-yl)heptanamine

63% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.84 (t, 3H), 1.26 (c, 6H), 1.76 (c, 2H), 1.84 (b, 2H), 2.49 (s, 3H), 3.0 (d, 2H), 3.13 (p, 1H), 7.1 (s, 1H), 7.18 (d, 1H), 7.6 (s, 1H), 7.74 (d, 1H).

PREPARATIVE EXAMPLE O2-(5-Chlorobenzo[b]thiophen-3-yl)-6,6,6-trifluorohexanamine

33% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.43-2.0 (c, 6H), 2.08 (m, 2H), 3.02 (c, 2H), 3.12 (m, 1H), 7.22 (s, 1H), 7.31, 7.32, 7.34, 7.35 (q, 1H), 7.75, 7.76, 7.77, 7.8 (q, 2H).

PREPARATIVE EXAMPLE P2-(5-Chlorobenzo[b]thiophen-3-yl)-6-methylheptanamine

69% yield

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<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79, 0.81, 0.82, 0.83 (2d, 6H), 1.1-1.33 (c, 4H), 1.47 (h, 1H), 1.62-1.93 (c, 4H), 3.01 (d, 2H), 3.11 (p, 1H), 7.2 (s, 1H), 7.29, 7.30, 7.32, 7.33 (q, 1H), 7.76, 7.77, 7.78, 7.784 (q, 2H).

#### PREPARATIVE EXAMPLE Q

##### 5      2-(Naphth-1-yl)-7,7-difluoroheptanamine

A mixture of 2-(naphth-1-yl)-7,7-difluoroheptanenitrile (413 mg, 1.51 mmol), Raney nickel (413 mg) and ammonia (0.9 g) in methanol (20 ml) was hydrogenated under 340 kPa (50 psi) hydrogen overnight at room temperature. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was partitioned between  
10 ethyl acetate (50 ml) and water (40 ml) and the ethyl acetate extract was washed with brine (30 ml), dried (sodium sulfate) and concentrated in vacuo. The residue (400 mg) was purified by column chromatography on silica gel (100 g), eluting with 85:15 ethyl acetate/methanol to yield the title compound as an oil (321 mg, 77% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.35 (c, 6H), 1.78 (c, 4H), 3.08 (c, 2H), 3.61 (c, 1H), 5.52, 5.71, 5.9  
15 (3t, total 1H), 7.37 (d, 1H), 7.5 (m, 3H), 7.75 (d, 1H), 7.88 (d, 1H), 8.16 (d, 1H).

The following compound was synthesized in a similar manner:

#### PREPARATIVE EXAMPLE R

##### 2-(2,5-Dimethylphenyl)-6-phenylhexanamine

74% yield

20      <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.15-1.44 (c, 4H), 1.5-1.75 (c, 4H), 2.29 (s, 3H), 2.32 (s, 3H), 2.55 (m, 2H), 2.9 (c, 3H), 6.91, 6.94, 6.95 (t, 2H), 7.05 (d, 1H), 7.14 (m, 3H), 7.29 (t, 2H).

#### EXAMPLE 1

##### 25      N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(4-isopropylbenzyl)urea

A solution of 2-(4-isopropylbenzylamino)indane (159 mg, 0.6 mmol) and 2,4-bis(methylthio)-6-methylpyridin-3-yl isocyanate (136 mg, 0.6 mmol) in 3 ml dimethylformamide was heated at 80°C under nitrogen overnight. The reaction mixture was cooled to room temperature, diluted with 50 ml ethyl acetate and washed with 3  
30 x 50 ml water, then 50 ml brine, dried (sodium sulfate), filtered and concentrated in vacuo. The solid residue (265 mg) was purified by column chromatography on silica gel (150 g), eluting with 7:3 hexane/ethyl acetate to yield the title compound as a white solid (195 mg, 66% yield).

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<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.25 (d, 6H), 2.36 (s, 3H), 2.45 (s, 3H), 2.47 (s, 3H), 2.91 (h, 1H), 3.06 (dd, 2H), 3.31 (dd, 2H), 4.57 (s, 2H), 5.39 (p, 1H), 5.57 (s, 1H), 6.59 (s, 1H), 7.15 (c, 4H), 7.22-7.35 (m, 4H).

The 1- and indan-2-yl urea derivatives of Examples 2-18 were synthesized in a similar manner.

#### EXAMPLE 2

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2,5-dimethylbenzyl)-N'-(indan-2-yl)urea

66% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.15 (s, 3H), 2.37 (s, 3H), 2.39 (s, 3H), 2.45 (s, 3H), 2.47 (s, 3H), 2.99 (dd, 2H), 3.29 (dd, 2H), 4.47 (s, 2H), 5.48 (s) and 5.50 (m) (total 2H), 6.58 (s, 1H), 7.04 (m, 2H), 7.15 (c, 5H), 7.43 (s, 1H).

#### EXAMPLE 3

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2,4-dimethylbenzyl)-N'-(indan-2-yl)urea

66% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.17 (s, 3H), 2.33 (s, 3H), 2.37 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 2.99 (dd, 2H), 3.26 (dd, 2H), 4.48 (s, 2H), 5.44 (m) and 5.49 (s) (total 2H), 6.58 (s, 1H), 6.99 (s, 1H), 7.14 (c, 5H), 7.47 (d, 1H).

#### EXAMPLE 4

N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(indan-2-yl)-N'-(4-isopropylbenzyl)urea

62% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.25 (d, 6H), 2.46 (s, 6H), 2.56 (s, 3H), 2.92 (h, 1H), 3.04 (dd, 2H), 3.31 (dd, 2H), 4.55 (s, 2H), 5.41 (m) and 5.46 (s) (total 2H), 7.16 (c, 4H), 7.23-7.34 (m, 4H).

#### EXAMPLE 5

N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(2,4-dimethylbenzyl)-N'-(indan-2-yl)urea

70% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.17 (s, 3H), 2.33 (s, 3H), 2.47 (s, 6H), 2.56 (s, 3H), 2.99 (dd, 2H), 3.28 (dd, 2H), 4.46 (s, 2H), 5.41 (s) and 5.44 (m) (total 2H), 6.99 (m, 1H), 7.14 (c, 5H), 7.44 (d, 1H).

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EXAMPLE 6N-(2,5-Dimethylbenzyl)-N-(indan-2-yl)-N'-(6-methylthioquinolin-5-yl)urea

19% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.20 (s, 3H), 2.45 (s, 6H), 3.06 (dd, 2H), 3.34 (dd, 2H), 4.60 (s, 2H), 5.54 (p, 1H), 6.20 (s, 1H), 7.07 (m, 2H), 7.16 (c, 4H), 7.38 (q, 1H), 7.46 (s, 1H), 7.60 (d, 1H), 7.96 (d, 1H), 8.07 (d, 1H), 8.82 (m, 1H).

EXAMPLE 7N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2-chlorobenzyl)-N'-(indan-2-yl)urea

17% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.38 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 3.02 (dd, 2H), 3.26 (dd, 2H), 4.67 (s, 2H), 5.37 (p, 1H), 5.51 (s, 1H), 6.59 (s, 1H), 7.14 (c, 4H), 7.25 (c, 1H), 7.38 (c, 2H), 7.64 (d, 1H).

EXAMPLE 8N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(2,5-dimethylbenzyl)-N'-(indan-2-yl)urea

69% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.15 (s, 3H), 2.39 (s, 3H), 2.47 (s, 6H), 2.57 (s, 3H), 2.98 (dd, 2H), 3.29 (dd, 2H), 4.45 (s, 2H), 5.40 (s, 1H), 5.50 (p, 1H), 7.06 (m, 2H), 7.14 (m, 4H), 7.38 (s, 1H).

EXAMPLE 9N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(indan-2-yl)-N'-[4-(3-methylbutyl)benzyl]urea

71% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.93 (d, 6H), 1.45-1.69 (c, 3H), 2.47 (s, 6H), 2.57 (s) and 2.61 (m) (total 5H), 3.03 (dd, 2H), 3.31 (dd, 2H), 4.55 (s, 2H), 5.40 (m) and 5.46 (m) (total 2H), 7.10-7.33 (c, 8H).

EXAMPLE 10N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-[4-(3-methylbutyl)benzyl]urea

58% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.92 (d, 6H), 1.44-1.68 (c, 3H), 2.36 (s, 3H), 2.44 (s, 3H), 2.46 (s, 3H), 2.60 (m, 2H), 3.04 (dd, 2H), 3.30 (dd, 2H), 4.56 (s, 2H), 5.39 (p, 1H), 5.54 (s, 1H), 6.58 (s, 1H), 7.10-7.34 (c, 8H).

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EXAMPLE 11

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(naphth-1-ylmethyl)urea

25% yield.

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.1 (c, 1H), 2.32-2.54 [total 10H, including 2.4 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H)], 2.83 (c, 2H), 4.69 (d, 1H), 5.26 (d, 1H), 5.5 (b, 1H), 6.06 (vb, 1H), 6.6 (s, 1H), 7.15-7.39 (c, 4H), 7.5 (c, 3H), 7.72-8.0 (c, 4H).

EXAMPLE 12

10 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(naphth-2-ylmethyl)urea

32% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.1 (c, 1H), 2.33-2.55 [total 10H, including 2.37 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H)], 2.88 (c, 2H), 4.5 (d, 1H), 4.8 (d, 1H), 5.6 (b, 1H), 6.08 (vb, 1H), 6.6 (s, 1H), 7.22 (c, 3H), 7.47-7.54 (c, 4H), 7.83 (c, 3H), 7.93 (s, 1H).

15 EXAMPLE 13

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(4-t-butylbenzyl)urea  
23% yield.

20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.32 (s, 9H), 2.1 (c, 1H), 2.36-2.55 [total 10H, including 2.38 (s, 3H), 2.46 (s, 3H), 2.48 (s, 3H)], 2.9 (c, 2H), 4.29 (d, 1H), 4.6 (d, 1H), 5.52 (b, 1H), 6.05 (vb, 1H), 6.6 (s, 1H), 7.22 (c, 4H), 7.32 (d, 2H), 7.39 (d, 2H).

EXAMPLE 14

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(4-phenylbenzyl)urea

28% yield.

25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.1 (c, 1H), 2.38-2.58 [total 10H, including 2.39 (s, 3H), 2.47 (s, 3H), 2.5 (s, 3H)], 2.9 (c, 2H), 4.4 (d, 1H), 4.7 (d, 1H), 5.54 (b, 1H), 6.02 (vb, 1H), 6.61 (s, 1H), 7.24 (c, 4H), 7.31-7.52 (c, 5H), 7.6 (c, 4H).

EXAMPLE 15

30 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(naphth-1-ylmethyl)urea

20% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.4 (s, 3H), 2.48 (s, 3H), 2.53 (s, 3H), 3.07 (dd, 2H), 3.33 (dd, 2H), 5.1 (s, 2H), 5.5 (m) and 5.57 (s) (total 2H), 6.6 (s, 1H), 7.12 (c, 4H), 7.48-7.64 (c, 3H), 7.76-7.97 (c, 4H).

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EXAMPLE 16

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(naphth-2-ylmethyl)urea

20% yield.

- 5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.37 (s, 3H), 2.48 (s, 6H), 3.1 (dd, 2H), 3.34 (dd, 2H), 4.78 (s, 2H), 5.47 (p, 1H), 5.68 (s, 1H), 6.6 (s, 1H), 7.15 (c, 4H), 7.38-7.58 (c, 3H), 7.87 (c, 3H), 7.95 (s, 1H).

EXAMPLE 17

10 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(2,4,6-trimethylbenzyl)urea

13% yield.

- <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.27 (s, 3H), 2.38 (s, 3H), 2.4 (s, 6H), 2.46 (s, 3H), 2.5 (s, 3H), 3.07 (dd, 2H), 3.55 (dd, 2H), 4.16 (m, 1H), 4.77 (s, 2H), 5.41 (s, 1H), 6.6 (s, 1H), 6.88 (s, 2H), 7.12 (c, 4H).

15

EXAMPLE 18

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2,3-dichlorobenzyl)-N'-(indan-2-yl)urea

27% yield.

- 20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.41 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 3.0 (dd, 2H), 3.28 (dd, 2H), 4.68 (s, 2H), 5.32 (q, 1H), 5.54 (s, 1H), 6.63 (s, 1H), 7.16 (c, 4H), 7.34 (t, 1H), 7.45 (d, 1H), 7.55 (d, 1H).

EXAMPLE 19

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(4-phenylbenzyl)urea

33% yield.

- 25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.28, 1.32 (2t, 6H), 1.4-1.8 (C, 10H), 2.02 (c, 2H), 2.42 (s, 3H), 2.86 (q, 2H), 3.09 (q, 2H), 4.37 (c, 1H), 4.62 (s, 2H), 5.54 (s, 1H), 6.62 (s, 1H), 7.34 (t, 1H), 7.44 (t, 2H), 7.51 (d, 2H), 7.6 (m, 4H).

EXAMPLE 20

30 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(fluoren-2-ylmethyl)urea

40% yield.

- <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.22, 1.24, 1.26, 1.27, 1.3 (2t, 6H), 1.4-1.8 (c, 10H), 2.02 (c, 2H), 2.41 (s, 3H), 2.84 (q, 2H), 3.06 (q, 2H), 3.91 (s, 2H), 4.42 (c, 1H), 4.65 (s, 2H), 5.55 (s, 1H), 6.6 (s, 1H), 7.25-7.44 (m, 3H), 7.54 (d, 1H), 7.68 (s, 1H), 7.78 (d, 2H).

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EXAMPLE 21

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(naphth-2-ylmethyl)urea

31% yield

- 5       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.2, 1.22, 1.25, 1.27, 1.3 (2t, 6H), 1.4-1.8 (c, 10H), 2.04 (c, 2H), 2.4 (s, 3H), 2.82 (q, 2H), 3.04 (q, 2H), 4.47 (c, 1H), 4.73 (s, 2H), 5.6 (s, 1H), 6.59 (s, 1H), 7.48 (c, 3H), 7.85 (m, 3H), 7.99 (s, 1H).

EXAMPLE 22

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-heptyl-N'-[naphth-2-ylmethyl]urea

- 10       33% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.86 (t, 3H), 1.2-1.42 (c, 14H), 1.72 (c, 2H), 2.43 (s, 3H), 2.88 (q, 2H), 3.11 (q, 2H), 3.44 (t, 2H), 4.79 (s, 2H), 5.73 (s, 1H), 6.65 (s, 1H), 7.48 (m, 3H), 7.85 (m, 4H).

EXAMPLE 23

- 15       N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-heptyl-N'-(2,4,6-trimethylbenzyl)urea  
34% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.86 (t, 3H), 1.23 (c, 8H), 1.3, 1.32, 1.33, 1.35, 1.36, 1.38 (2t, 6H), 1.65 (c, 2H), 2.27 (s, 3H), 2.36 (s, 6H), 2.46 (s, 3H), 2.91 (q, 2H), 3.05 (t, 2H), 3.15 (q, 2H), 4.71 (s, 2H), 5.7 (s, 1H), 6.68 (s, 1H), 6.87 (s, 2H).

20

EXAMPLE 24

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(4-phenylbenzyl)urea  
17% yield.

- 25       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.4-1.77 (c, 10H), 2.02 (c, 2H), 2.36 (s, 3H), 2.45 (s, 3H), 2.46 (s, 3H), 4.38 (c, 1H), 4.62 (s, 2H), 5.51 (s, 1H), 6.58 (s, 1H), 7.34 (t, 1H), 7.4-7.54 (m, 4H), 7.61 (t, 4H).

EXAMPLE 25

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(fluoren-2-ylmethyl)urea

9% yield.

- 30       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.4-1.8 (c, 10H), 2.02 (c, 2H), 2.35 (s, 3H), 2.43 (s, 3H), 2.44 (s, 3H), 3.91 (s, 2H), 4.42 (c, 1H), 4.66 (s, 1H), 5.52 (s, 1H), 6.57 (s, 1H), 7.24-7.45 (m, 3H), 7.55 (d, 1H), 7.67 (s, 1H), 7.79 (d, 2H).

EXAMPLE 26



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N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(4-isopropylbenzyl)-N'-(1,2,3,4-tetrahydronaphth-2-yl)urea

13% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.25, 1.26, 1.27, 1.29, 1.31, 1.34, 1.36 (2t and d, 12H), 1.88 (m, 1H), 2.13 (c, 1H), 2.42 (s, 3H), 2.8-3.02 (m and q, 6H), 3.02-3.18 (c and q, 3H), 4.61 (s, 2H), 4.78 (c, 1H), 5.62 (s, 1H), 6.63 (s, 1H), 7.08 (s, 4H), 7.26 (d, 2H), 7.4 (d, 2H).

EXAMPLE 27

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-heptyl-N'-(3-methylbenzo[b]thiophen-2-ylmethyl)urea

35% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.87 (t, 3H), 1.29-1.9 [c including 2t (1.26, 1.28, 1.29, 1.31, 1.32), total 14H], 1.75 (c, 2H), 2.42 (s, 3H), 2.45 (s, 3H), 2.88 (q, 2H), 3.11 (q, 2H), 3.36 (t, 2H), 4.86 (s, 2H), 5.77 (s, 1H), 6.67 (s, 1H), 7.28-7.4 (m, 2H), 7.66 (d, 1H), 7.79 (d, 1H).

EXAMPLE 28

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(1,2,3,4-tetrahydronaphth-2-yl)-N'-(2,4,6-trimethylbenzyl)urea

26% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.32, 1.36 (2t, 6H), 2.06 (c, 1H), 2.15-2.35 [c and s (2.25), total 4H], 2.42 (s, 6H), 2.44 (s, 3H), 2.6-2.96 (c, 5H), 3.14 (q, 2H), 3.42 (m, 1H), 3.73 (c, 1H), 4.74 (s, 2H), 5.75 (s, 1H), 6.66 (s, 1H), 6.84 (s, 2H), 7.06 (c, 4H).

EXAMPLE 29

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cycloheptyl-N'-(naphth-2-ylmethyl)urea

18% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.49-1.74 (c, 10H), 2.04 (c, 2H), 2.33 (s, 3H), 2.43 (s, 6H), 4.45 (c, 1H), 4.74 (s, 2H), 5.57 (s, 1H), 6.56 (s, 1H), 7.48 (c, 3H), 7.85 (c, 3H), 7.97 (s, 1H).

EXAMPLE 30

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(4-isopropylbenzyl)urea

17% yield

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<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.26 (d) and 1.29, 1.34 (2t) (total 12H), 2.42 (s, 3H), 2.82-2.98 (m, 3H), 3.0-3.14 (m, 4H), 3.31 (dd, 2H), 4.57 (s, 2H), 5.41 (p, 1H), 5.58 (s, 1H), 6.63 (s, 1H), 7.15 (c, 4H), 7.25 (d, 2H), 7.33 (d, 2H).

EXAMPLE 31

5        N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(2,4-dimethylbenzyl)-N'-(indan-2-yl)urea

43% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.31, 1.35 (2t, 6H), 2.18 (s, 3H), 2.33 (s, 3H), 2.43 (s, 3H), 2.89 (q, 2H), 3.0 (dd, 2H), 3.11 (q, 2H), 3.29 (dd, 2H), 4.49 (s, 2H), 5.44 (p, 1H),  
10 5.52 (s, 1H), 6.63 (s, 1H), 6.99 (s, 1H), 7.1-7.2 (c, 5H), 7.49 (d, 1H).

EXAMPLE 32

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(4-isopropylbenzyl)-N'-(6,7,8,9-tetrahydro-5H-benzocyclohepten-7-yl)urea

39% yield

15        <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.24 (d, 6H), 1.45-1.6 (m, 2H), 2.22 (c, 2H), 2.36 (s, 3H), 2.46 (s, 3H), 2.7-2.96 (m, 6H), 4.45 (s, 2H), 4.72 (c, 1H), 5.52 (s, 1H), 6.59 (s, 1H), 7.1 (m, 4H), 7.23 (d, 2H), 7.31 (d, 2H).

EXAMPLE 33

20        N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(2,4,6-trimethylbenzyl)urea

27% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.3, 1.34 (2t, 6H), 2.27 (s, 3H), 2.4 (s, 6H), 2.41 (s, 3H), 2.88 (q, 2H), 2.98-3.18 (m, 4H), 3.57 (dd, 2H), 4.16 (p, 1H), 4.77 (s, 2H), 5.43 (s, 1H), 6.62 (s, 1H), 6.87 (s, 2H), 7.11 (c, 4H).

25

EXAMPLE 34

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2,2-diphenylethyl]urea

A solution of 2,2-diphenylethylamine (148 mg, 0.75 mmol) and 2,4-bis(methylthio)-6-methylpyridin-3-yl isocyanate (170 mg, 0.75 mmol) in 15 ml dichloromethane was refluxed under nitrogen overnight. The reaction mixture was then  
30 cooled to room temperature and concentrated in vacuo. The residual solid was purified by column chromatography on silica gel (200 g), eluting with 8:2 dichloromethane/ethyl acetate to yield the title compound as white solid (111 mg, 35% yield).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.29 (s, 3H), 2.46 (s, 3H), 2.50 (s, 3H), 3.82 (q, 2H), 4.18 (t, 1H), 6.53 (s, 1H), 7.12-7.28 (c, 12H).

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The (2,2-diphenylethyl)urea derivatives of Examples 35-37 were prepared according to the method of Example 34.

**EXAMPLE 35**N-(2,2-Diphenylethyl)-N'-(6-methylthioquinolin-5-yl)urea

5 63% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.27 (s, 3H), 3.62 (bd, 2H), 3.98 (t, 1H), 6.39 (b, 1H), 6.88-7.08 (c, 10H), 7.54 (q, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 8.27 (d, 1H), 8.39 (d, 1H), 8.64 (m, 1H).

**EXAMPLE 36**

10 N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(2,2-diphenylethyl)urea

80% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.42 (s, 6H), 2.60 (s, 3H), 3.82 (bm, 2H), 4.19 (t, 1H), 4.50 (b, 1H), 5.07 (b, 1H), 7.09-7.27 (c, 10H).

**EXAMPLE 37**

15 N-[4,6-Bis(methylthio)pyrimidin-5-yl]-N'-(2,2-diphenylethyl)urea

49% yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ 2.43 (s, 3H), 3.84 (q, 2H), 4.20 (t, 1H), 4.43 (c, 1H), 5.46 (s, 1H), 7.12-7.31 (c, 10H), 8.59 (s, 1H).

**EXAMPLE 38**

20 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(1-phenylcyclopentyl)methylurea

A solution of (1-phenylcyclopentyl)methylamine (140 mg, 0.8 mmol) and 2,4-bis(methylthio)-6-methylpyridin-3-yl isocyanate (180 mg, 0.8 mmol) in 3 ml dimethylformamide was heated at 80°C under nitrogen overnight. The reaction mixture was cooled to room temperature and diluted with 70 ml ethyl acetate. The resulting  
25 solution was washed with 3 x 60 ml water and 60 ml brine, dried (sodium sulfate), filtered and concentrated in vacuo. The residue was chromatographed on silica gel (200 g), eluting with 1:1 ethyl acetate/hexane to yield the title compound as a white solid (90 mg, 28% yield).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.6-1.9 (c, 6H), 2.03 (c, 2H), 2.35 (s, 3H), 2.49 (s,  
30 3H), 2.51 (s, 3H), 3.27 (d, 2H), 4.07 (b, 1H), 5.38 (b, 1H), 6.55 (s, 1H), 7.12 (c, 5H).

The urea derivatives of Examples 39-46 were prepared according to the method of Example 38.

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EXAMPLE 39N-(6-Methylthioquinolin-5-yl)-N'-[(1-phenylcyclopentyl)methyl]urea

31% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.59-1.96 (c, 8H), 2.50 (s, 3H), 3.25 (d, 2H), 3.91 (b, 1H), 5.96 (bs, 1H), 6.81 (c, 2H), 6.95 (c, 3H), 7.41 (q, 1H), 7.57 (d, 1H), 8.05 (d, 1H), 8.22 (d, 1H), 8.86 (m, 1H).

EXAMPLE 40N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[{1-(4-methylphenyl)cyclopentyl}]methyl]urea

24% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.6-1.9 (c, 6H), 2.0 (c, 2H), 2.27 (s, 3H), 2.35 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 3.24 (d, 2H), 4.06 (b, 1H), 5.36 (b, 1H), 6.51 (s, 1H), 6.98 (q, 4H).

EXAMPLE 41N-[{1-(4-Methylphenyl)cyclopentyl}]methyl]-N'-(6-methylthioquinolin-5-yl)urea

28% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.6-1.98 (c, 8H), 2.19 (s, 3H), 2.52 (s, 3H), 3.25 (d, 2H), 3.98 (b, 1H), 5.95 (b, 1H), 6.74 (q, 4H), 7.43 (q, 1H), 7.60 (d, 1H), 8.11 (d, 1H), 8.24 (d, 1H), 8.87 (m, 1H).

EXAMPLE 42N-(6-Methylthioquinolin-5-yl)-N'-[(1-phenylcyclohexyl)methyl]urea

37% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.18-1.62 (c, 8H), 1.96 (c, 2H), 2.51 (s, 3H), 3.25 (d, 2H), 3.86 (b, 1H), 5.99 (b, 1H), 6.97 (c, 5H), 7.43 (q, 1H), 7.58 (d, 1H), 8.09 (d, 1H), 8.23 (d, 1H), 8.85 (m, 1H).

EXAMPLE 43N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(1-phenylcyclohexyl)methyl]urea

42% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.22-1.72 (c, 8H), 2.08 (c, 2H), 2.35 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.25 (d, 2H), 3.95 (b, 1H), 5.38 (b, 1H), 6.51 (s, 1H), 7.05-7.25 (c, 5H).

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EXAMPLE 44N-[[1-(4-Methylphenyl)cyclohexyl]methyl]-N'-(6-methylthioquinolin-5-yl)urea

42% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.15-1.6 (c, 8H), 1.93 (c, 2H), 2.18 (s, 3H), 2.51 (s, 3H), 3.22 (d, 2H), 3.81 (b, 1H), 5.94 (b, 1H), 6.77 (b, 4H), 7.41 (q, 1H), 7.59 (d, 1H), 8.07 (d, 1H), 8.21 (d, 1H), 8.86 (m, 1H).

EXAMPLE 45N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-[[1-(4-methylphenyl)cyclohexyl]methyl]urea

42% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.23-1.68 (c, 8H), 2.06 (c, 2H), 2.30 (s, 3H), 2.47 (s, 6H), 2.62 (s, 3H), 3.23 (d, 2H), 3.89 (b, 1H), 5.27 (b, 1H), 7.04 (q, 4H).

EXAMPLE 46N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[[1-(4-methylphenyl)cyclohexyl]methyl]urea

24% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.2-1.7 (c, 8H), 2.06 (c, 2H), 2.28 (s, 3H), 2.35 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.22 (d, 2H), 3.95 (b, 1H), 5.38 (b, 1H), 6.56 (s, 1H), 7.03 (q, 4H).

EXAMPLE 47N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-ethyl-2-phenyl)butyl]urea

A solution of 2-ethyl-2-phenylbutylamine (106 mg, 0.6 mmol) and 2,4-bis(methylthio)-6-methylpyridin-3-yl isocyanate (136 mg, 0.6 mmol) in 3 ml dimethylformamide was heated at 80°C under nitrogen overnight. The reaction mixture was cooled to room temperature and diluted with 50 ml ethyl acetate. The resulting solution was washed sequentially with 3 x 25 ml water and 25 ml brine, dried (sodium sulfate), filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (125 g), eluting with 65:35 hexane/ethyl acetate to yield the title compound as a white solid (67 mg, 28% yield).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.74 (t, 6H), 1.57-1.8 (c, 4H), 2.33 (s, 3H), 2.47 (s, 3H), 2.48 (s, 3H), 3.41 (d, 2H), 3.95 (b, 1H), 5.36 (b, 1H), 6.52 (s, 1H), 7.05-7.27 (c, 5H).

The urea derivatives of Examples 48-55 were prepared according to the method of Example 47.

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EXAMPLE 48N-[2,4-Bis(isopropylthio)-6-methylpyridin-3-yl]-N'-[(2-ethyl-2-phenyl)butyl]urea

35% yield.

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.72 (t, 6H), 1.29 (d, 6H), 1.33 (d, 6H), 1.57-1.8 (c, 4H), 2.45 (s, 3H), 3.39 (d and m, 3H), 3.93 (m and b, 2H), 5.28 (b, 1H), 6.58 (s, 1H), 7.04-7.2 (c, 5H).

EXAMPLE 49N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-ethyl-2-{2-methylphenyl})butyl]urea

10 33% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.74 (t, 6H), 1.67 (m, 4H), 2.28 (s, 3H), 2.33 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H), 3.4 (d, 2H), 3.97 (b, 1H), 5.35 (b, 1H), 6.53 (s, 1H), 6.94 (t, 1H), 6.98 (s, 2H), 7.08 (t, 1H).

EXAMPLE 5015 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-phenyl-2-propyl)pentyl]urea

88% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.85 (t, 6H), 0.88-1.3 (c, 4H), 1.59 (c, 4H), 2.32 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H), 3.4 (d, 2H), 3.96 (b, 1H), 5.33 (b, 1H), 6.52 (s, 1H), 7.05-7.24 (c, 5H).

20

EXAMPLE 51N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2-methylphenyl}-2-propyl)pentyl]urea

43% yield.

25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.84 (t, 6H), 0.96-1.3 (c, 4H), 1.58 (c, 4H), 2.27 (s, 3H), 2.32 (s, 3H), 2.46 (s, 3H), 2.47 (s, 3H), 3.39 (d, 2H), 3.96 (b, 1H), 5.3 (s, 1H), 6.52 (s, 1H), 6.93 (t, 1H), 6.97 (s, 2H), 7.06 (t, 1H).

EXAMPLE 52N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2-methylphenyl}-2-butyl)hexyl]urea

30 57% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.84 (t, 6H), 0.94-1.33 (c, 8H), 1.59 (c, 4H), 2.27 (s, 3H), 2.32 (s, 3H), 2.46 (s, 3H), 2.48 (s, 3H), 3.4 (d, 2H), 3.96 (b, 1H), 5.29 (s, 1H), 6.53 (s, 1H), 6.93 (c, 3H), 7.07 (t, 1H).

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EXAMPLE 53

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,5-dimethoxyphenyl})-2-propyl]pentyl]urea

30% yield.

- 5       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 6H), 0.94-1.3 (c, 4H), 1.5-1.8 (c, 4H), 2.33 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 3.6 (d, 2H), 3.68 (s, 3H), 3.74 (s, 3H), 4.11 (b, 1H), 5.38 (b, 1H), 6.5 (s, 1H), 6.64 (s and m, total 3H).

EXAMPLE 54

- 10       N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,3-dimethoxyphenyl})-2-propyl]pentyl]urea

45% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 6H), 0.98-1.25 (c, 4H), 1.67 (c, 4H), 2.32 (s, 3H), 2.44 (s, 3H), 2.47 (s, 3H), 3.59 (d, 2H), 3.78 (s, 3H), 3.82 (s, 3H), 4.08 (b, 1H), 5.33 (b, 1H), 6.51 (s, 1H), 6.66 (d, 1H), 6.77 (d, 1H), 6.84 (t, 1H).

15

EXAMPLE 55

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,5-dimethylphenyl})-2-propyl]pentyl]urea

30% yield.

- 20       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 6H), 1.08 (m, 4H), 1.65 (c, 4H), 2.22 (s, 3H), 2.32 (s, 3H), 2.38 (s, 3H), 2.45 (s, 3H), 2.46 (s, 3H), 3.57 (d, 2H), 4.04 (b, 1H), 5.37 (b, 1H), 6.49 (s, 1H), 6.85 (c, 3H).

EXAMPLE 56

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2-methylphenyl)hexyl]urea

- 25       A solution of 2-(2-methylphenyl)hexylamine (153 mg, 0.8 mmol) and 2,4-bis(methylthio)-6-methylpyridin-3-yl isocyanate (180 mg, 0.8 mmol) in 3 ml dimethylformamide was heated at 80°C under nitrogen overnight. The reaction mixture was cooled to room temperature and diluted with 60 ml ethyl acetate. The resulting solution was washed sequentially with 3 x 50 ml water and 50 ml brine, dried (sodium sulfate), filtered and concentrated in vacuo. The residue was chromatographed on silica gel (200 g), eluting with 7:3 hexane/ethyl acetate to yield the title compound as  
30       a white solid (110 mg, 33% yield).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.80 (t, 3H), 1.06-1.32 (c, 4H), 1.46-1.74 (c, 2H), 2.23 (s, 3H), 2.30 (s, 3H), 2.43 (s, 3H), 2.48 (s, 3H), 3.03-3.26 (c, 2H), 3.51 (p, 1H), 4.21 (b, 1H), 5.33 (b, 1H), 6.52 (s, 1H), 7.01-7.11 (c, 4H).

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The urea derivatives of Examples 57-82 were prepared according to the method of Example 56.

**EXAMPLE 57**

N-[2-(2-Methylphenyl)hexyl]-N'-(6-methylthioquinolin-5-yl)urea

5 28% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.80 (t, 3H) 0.98-1.28 (c, 4H), 1.4-1.65 (c, 2H), 2.08 (s, 3H), 2.48 (s, 3H), 2.96-3.27 (c, 2H), 3.51 (p, 1H), 4.10 (b, 1H), 5.94 (b, 1H), 6.87-7.02 (c, 4H), 7.36 (q, 1H), 7.57 (d, 1H), 8.06 (d, 1H), 8.14 (d, 1H), 8.82 (m, 1H).

**EXAMPLE 58**

10 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2-(4-methylphenyl)heptyl)urea

24% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.80 (t, 3H), 1.07-1.28 (c, 6H), 1.45-1.7 (c, 2H), 2.28 (s, 3H), 2.32 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 2.65 (c, 1H), 3.10 (c, 1H), 3.56 (p, 1H), 4.21 (b, 1H), 5.35 (b, 1H), 6.54 (s, 1H), 6.98 (q, 4H).

15

**EXAMPLE 59**

N-[2-(4-Methylphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea

30% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79 (t, 3H), 1.02-1.26 (c, 6H), 1.46-1.62 (c, 2H), 2.23 (s, 3H), 2.48 (s, 3H), 2.57 (c, 1H), 3.10 (c, 1H), 3.56 (p, 1H), 4.11 (b, 1H), 5.96 (s, 1H), 6.81 (q, 4H), 7.34 (q, 1H), 7.57 (d, 1H), 8.04 (d, 1H), 8.13 (d, 1H), 8.82 (m, 1H).

20

**EXAMPLE 60**

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2-(3-methylphenyl)heptyl)urea

26% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.06-1.32 (c, 6H), 1.45-1.72 (c, 2H), 2.28 (s, 3H), 2.34 (s, 3H), 2.48 (s, 3H), 2.50 (s, 3H), 2.67 (c, 1H), 3.14 (m, 1H), 3.57 (p, 1H), 4.31 (b, 1H), 5.47 (b, 1H), 6.56 (s, 1H), 6.87 (d, 1H), 6.89 (s, 1H), 6.96 (d, 1H), 7.09 (t, 1H).

25

**EXAMPLE 61**

N-[2-(3-Methylphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea

30 24% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.8 (t, 3H) 1.0-1.3 (c, 6H), 1.37-1.64 (c, 2H), 2.19 (s, 3H), 2.48 (s, 3H), 2.59 (c, 1H), 3.14 (m, 1H), 3.57 (p, 1H), 4.23 (b, 1H), 6.11 (b, 1H), 6.7 (d, 1H), 6.72 (s, 1H), 6.88 (d, 1H), 6.97 (t, 1H), 7.35 (q, 1H), 7.56 (d, 1H), 8.04 (d, 1H), 8.14 (d, 1H), 8.81 (m, 1H).



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EXAMPLE 62N-[2-(3-Methylphenyl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea

53% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.8 (t, 3H), 1.04-1.28 (c, 6H), 1.38-1.63 (c, 2H), 2.21 (s, 3H), 2.6 (m, 1H), 3.13 (m, 1H), 3.59 (m, 1H), 3.9 (s, 3H), 4.22 (b, 1H), 5.98 (b, 1H), 6.71 (d, 1H), 6.73 (s, 1H), 6.91 (d, 1H), 7.01 (t, 1H), 7.31 (q, 1H), 7.46 (d, 1H), 8.07 (d, 1H), 8.18 (d, 1H), 8.77 (m, 1H).

EXAMPLE 63N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)hexyl]urea

32% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.04-1.32 (c, 4H), 1.45-1.74 (c, 2H), 2.18 (s, 3H), 2.23 (s, 3H), 2.31 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.04 (m, 1H), 3.2 (m, 1H), 3.53 (p, 1H), 4.2 (b, 1H), 5.34 (b, 1H), 6.53 (s, 1H), 6.84 (d, 1H), 6.93 (d, 1H).

EXAMPLE 64N-[2-(2,5-Dimethylphenyl)hexyl]-N'-(6-methylthioquinolin-5-yl)urea

33% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>) δ 0.76 (t, 3H), 1.0-1.26 (c, 4H), 1.35-1.65 (c, 2H), 2.1 (s, 3H), 2.17 (s, 3H), 2.44 (s, 3H), 3.0 (c, 1H), 3.15 (m, 1H), 3.56 (p, 1H), 4.96 (b, 1H), 6.74-6.92 [total 4H, including 6.78 (d, 1H), 6.81 (s, 1H), 6.87 (d, 1H and 20 b)], 7.34 (q, 1H), 7.56 (d, 1H), 8.02 (d, 1H), 8.16 (d, 1H), 8.76 (m, 1H).

EXAMPLE 65N-[2-(2,5-Dimethylphenyl)hexyl]-N'-(6-methoxyquinolin-5-yl)urea

37% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>) δ 0.76 (t, 3H), 1.0-1.28 (c, 4H), 1.35-1.64 (c, 2H), 2.07 (s, 3H), 2.17 (s, 3H), 3.0 (c, 1H), 3.11 (m, 1H), 3.57 (p, 1H), 3.86 (s, 3H), 4.71 (b, 1H), 6.46 (b, 1H), 6.77 (s, 1H), 6.78 (d, 1H), 6.86 (d, 1H), 7.28 (q, 1H), 7.42 (d, 1H), 8.0 (d, 1H), 8.16 (d, 1H), 8.71 (m, 1H).

EXAMPLE 66N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)heptyl]urea

28% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.08-1.3 (c, 6H), 1.43-1.74 (c, 2H), 2.19 (s, 3H), 2.23 (s, 3H), 2.33 (s, 3H), 2.48 (s, 3H), 2.53 (s, 3H), 3.04 (c, 1H), 3.21 (m, 1H), 3.51 (p, 1H), 4.35 (b, 1H), 5.0 (b, 1H), 6.56 (s, 1H), 6.84 (d, 1H), 6.86 (d, 1H), 6.93 (d, 1H).

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**EXAMPLE 67**N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,4-dimethylphenyl)hexyl]urea

68% yield.

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.05-1.31 (c, 4H), 1.42-1.75 (c, 2H), 2.2 (s, 3H), 2.26 (s, 3H), 2.32 (s, 3H), 2.46 (s, 3H), 2.52 (s, 3H), 3.04 (c, 1H), 3.18 (m, 1H), 3.49 (p, 1H), 4.3 (b, 1H), 5.46 (b, 1H), 6.55 (s, 1H), 6.86 (s, 1H), 6.89 (d, 1H), 6.95 (d, 1H).

**EXAMPLE 68**N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3-methylphenyl)hexyl]urea

10 60% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.05-1.33 (c, 4H), 1.45-1.75 (c, 2H), 2.28 (s, 3H), 2.34 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 2.67 (m, 1H), 3.15 (m, 1H), 3.57 (p, 1H), 4.34 (b, 1H), 5.48 (b, 1H), 6.57 (s, 1H), 6.88 (d, 1H), 6.89 (s, 1H), 6.96 (d, 1H), 7.1 (t, 1H).

**EXAMPLE 69**N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,4-dimethylphenyl)heptyl]urea

59% yield.

15 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.08-1.28 (c, 6H), 1.42-1.72 (c, 2H), 2.19 (s, 3H), 2.26 (s, 3H), 2.32 (s, 3H), 2.45 (s, 3H), 2.51 (s, 3H), 3.04 (c, 1H), 3.18 (m, 1H), 3.49 (p, 1H), 4.24 (b, 1H), 5.38 (b, 1H), 6.55 (s, 1H), 6.86 (s, 1H), 6.89 (d, 1H), 6.95 (d, 1H).

**EXAMPLE 70**N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)heptyl]urea

50% yield.

25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79 (t, 3H), 1.14-1.34 (c, 6H), 1.56-1.92 (c, 2H), 2.14 (s, 3H), 2.38 (s, 3H), 2.44 (s, 3H), 3.48 (m, 1H), 3.6 (p, 1H), 3.73 (c, 1H), 4.26 (b, 1H), 5.37 (b, 1H), 6.39 (s, 1H), 7.28 (d, 1H), 7.36 (t, 1H), 7.47 (c, 2H), 7.67 (d, 1H), 7.82 (c, 1H), 8.13 (c, 1H).

**EXAMPLE 71**N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-2-yl)hexyl]urea

36% yield.

30 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.8 (t, 3H), 1.06-1.35 (c, 4H), 1.55-1.81 (c, 2H), 2.07 (s, 3H), 2.37 (s, 3H), 2.4 (s, 3H), 2.9 (c, 1H), 3.24 (m, 1H), 3.66 (p, 1H), 4.25 (b, 1H), 5.39 (b, 1H), 6.34 (s, 1H), 7.25 (m, 1H), 7.4-7.51 (c, 3H), 7.68-7.87 (c, 3H).

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EXAMPLE 72N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)hexyl]urea

36% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79 (t, 3H), 1.1-1.34 (c, 4H), 1.56-1.92 (c, 2H), 2.13 (s, 3H), 2.37 (s, 3H), 2.44 (s, 3H), 3.47 (m, 1H), 3.6 (p, 1H), 3.73 (c, 1H), 4.28 (b, 1H), 5.36 (b, 1H), 6.4 (s, 1H), 7.28 (d, 1H), 7.35 (t, 1H), 7.46 (c, 2H), 7.66 (d, 1H), 7.82 (c, 1H), 8.12 (c, 1H).

EXAMPLE 73N-(6-Methylthioquinolin-5-yl)-N'-[2-(naphth-1-yl)hexyl]urea

34% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78 (t, 3H), 1.1-1.3 (c, 4H), 1.56-1.82 (c, 2H), 2.35 (s, 3H), 3.44 (c, 1H), 3.7 (c, 2H), 4.21 (b, 1H), 5.98 (s, 1H), 7.08 (c, 2H), 7.22 (t, 1H), 7.42 (c, 3H), 7.6 (d, 1H), 7.8 (d, 1H), 7.9 (d, 1H), 7.94 (d, 1H), 8.03 (d, 1H), 8.7 (m, 1H).

EXAMPLE 74

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,3-dimethoxyphenyl)heptyl]urea

29% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.1-1.3 (c, 6H), 1.45-1.77 (c, 2H), 2.33 (s, 3H), 2.48 (s, 3H), 2.53 (s, 3H), 3.12-3.35 (c, 2H), 3.45 (p, 1H), 3.69 (s, 3H), 3.84 (s, 3H), 4.54 (b, 1H), 5.52 (b, 1H), 6.59 (s, 1H), 6.7 (d, 1H), 6.73 (d, 1H), 6.95 (t, 1H).

EXAMPLE 75N-[2-(2,3-Dimethoxyphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea

31% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.05-1.3 (c, 6H), 1.42-1.65 (c, 2H), 2.49 (s, 3H), 3.12 (c, 1H), 3.27 (c, 1H), 3.46 (m, 1H), 3.53 (s, 3H), 3.8 (s, 3H), 4.44 (b, 1H), 6.04 (b, 1H), 6.56 (d, 1H), 6.66 (d, 1H), 6.85 (t, 1H), 7.37 (q, 1H), 7.61 (d, 1H), 8.08 (d, 1H), 8.17 (d, 1H), 8.82 (m, 1H).

EXAMPLE 76N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3-methylphenyl)octyl]urea

47% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 3H), 1.19 (b, 8H), 1.46-1.72 (c, 2H), 2.27 (s, 3H), 2.33 (s, 3H), 2.46 (s, 3H), 2.48 (s, 3H), 2.66 (c, 1H), 3.13 (c, 1H), 3.58 (p, 1H), 4.23 (b, 1H), 5.35 (s, 1H), 6.55 (s, 1H), 6.87 (d) and 6.88 (s) (total 2H), 6.96 (d, 1H), 7.09 (t, 1H).

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EXAMPLE 77N-[2-(3-Methylphenyl)octyl]-N'-(6-methoxyquinolin-5-yl)urea

54% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 3H), 1.18 (b, 8H), 1.53 (c, 2H), 2.22 (s, 3H),  
5 2.61 (m, 1H), 3.14 (m, 1H), 3.6 (p, 1H), 3.91 (s, 3H), 4.24 (b, 1H), 5.99 (s, 1H), 6.72 (d)  
and 6.73 (s) (total 2H), 6.92 (d, 1H), 7.01 (t, 1H), 7.33 (q, 1H), 7.47 (d, 1H), 8.09 (d, 1H),  
8.19 (d, 1H), 8.77 (q, 1H).

EXAMPLE 78N-[2-(3-Methylphenyl)octyl]-N'-(6-methylthioquinolin-5-yl)urea

25% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 3H), 1.17 (b, 8H), 1.52 (c, 2H), 2.2 (s, 3H),  
2.49 (s, 3H), 2.6 (m, 1H), 3.15 (m, 1H), 3.58 (p, 1H), 4.21 (b, 1H), 6.05 (s, 1H), 6.71 (d)  
and 6.73 (s) (total 2H), 6.89 (d, 1H), 6.99 (t, 1H), 7.37 (q, 1H), 7.58 (d, 1H), 8.07 (d, 1H),  
8.17 (d, 1H), 8.82 (t, 1H).

EXAMPLE 79N-[2-(naphth-1-yl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea

58% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.19 (b, 6H), 1.7 (b, 2H), 3.41 (c, 1H),  
3.72 (c) and 3.75 (s) (total 5H), 4.21 (b, 1H), 5.88 (s, 1H), 7.02 (q, 1H), 7.13 (d, 1H),  
20 7.25 (t, 1H), 7.33 (d, 1H), 7.45 (m, 2H), 7.63 (d, 1H), 7.83 (d, 1H), 7.92 (d, 1H), 7.98 (d,  
1H), 8.04 (d, 1H), 8.65 (m, 1H).

EXAMPLE 80N-[2-(naphth-1-yl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea

47% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.17 (b, 6H), 1.7 (b, 2H), 2.35 (s, 3H),  
3.44 (c, 1H), 3.6-3.78 (c, 2H), 4.22 (b, 1H), 5.97 (s, 1H), 7.06 (q, 1H), 7.12 (d, 1H), 7.23  
(t, 1H), 7.43 (m, 3H), 7.6 (d, 1H), 7.81 (d, 1H), 7.9 (d, 1H), 7.96 (d, 1H), 8.03 (d, 1H),  
25 8.69 (m, 1H).

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EXAMPLE 81N-[2-(2,4-Dimethylphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea

41% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79 (t, 3H), 1.14 (b, 6H), 1.48 (c, 2H), 2.0 (s, 3H),  
5 2.2 (s, 3H), 2.47 (s, 3H), 2.95 (c, 1H), 3.15 (m, 1H), 3.5 (p, 1H), 4.06 (b, 1H), 5.91 (s,  
1H), 6.71 (s, 1H), 6.75 (s, 2H), 7.32 (q, 1H), 7.55 (d, 1H), 8.03 (d, 1H), 8.03 (d, 1H),  
8.11 (d, 1H), 8.82 (q, 1H).

EXAMPLE 82N-[2-(2,4-Dimethylphenyl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea

10 57% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.8 (t, 3H), 1.16 (b, 6H), 1.49 (c, 2H), 2.02 (s, 3H),  
2.23 (s, 3H), 2.97 (c, 1H), 3.13 (m, 1H), 3.55 (p, 1H), 3.9 (s, 3H), 4.14 (b, 1H), 5.89 (s,  
1H), 6.75 (s, 1H), 6.78 (s, 2H), 7.28 (q, 1H), 7.44 (d, 1H), 8.04 (d, 1H), 8.14 (d, 1H),  
8.77 (q, 1H).

15

EXAMPLE 83N-[2,4-Bis(methyl)-6-methylpyridin-3-yl]-N'-[2-(3,4,5-trimethoxyphenyl)heptyl]urea

45% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 3H), 1.23 (b, 6H), 1.4-1.7 (c, 2H), 2.3 (s,  
3H), 2.45 (s, 3H), 2.48 (s, 3H), 2.64 (c, 1H), 3.12 (m, 1H), 3.57 (q, 1H), 3.79 (s, 6H),  
20 3.82 (s, 3H), 4.23 (b, 1H), 5.39 (b, 1H), 6.27 (s, 2H), 6.54 (s, 1H).

EXAMPLE 84

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethyl-4-methoxyphenyl)heptyl]urea

35% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.19 (b, 6H), 1.5 (c, 1H), 1.63 (c, 1H),  
25 2.11 (s, 3H), 2.2 (s, 3H), 2.34 (s, 3H), 2.49 (s, 3H), 2.54 (s, 3H), 2.98 (c, 1H), 3.18 (m,  
1H), 3.49 (p, 1H), 3.79 (s, 3H), 4.2 (b, 1H), 5.35 (b, 1H), 6.5 (s, 1H), 6.58 (s, 1H), 6.79  
(s, 1H).

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EXAMPLE 85

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethoxyphenyl)heptyl]urea

40% yield.

5       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.2 (b, 6H), 1.63 (b, 2H), 2.34 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 3.15 (c, 1H), 3.26-3.5 (c, 2H), 3.62 (s, 3H), 3.73 (s, 3H), 4.48 (b, 1H), 5.54 (b, 1H), 6.58 (s, 1H), 6.61-6.71 (c, 3H).

EXAMPLE 86

N-2-(2,5-Dimethoxyphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea

10       30% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.17 (b, 6H), 1.54 (b, 2H), 2.49 (s, 3H), 3.08 (c, 1H), 3.24-3.4 (m including s at 3.38, total 4H), 3.45 (p, 1H), 3.72 (s, 3H), 4.42 (b, 1H), 6.05 (b, 1H), 6.49 (d, 1H), 6.52-6.61 (c, 2H), 7.35 (q, 1H), 7.61 (d, 1H), 8.09 (d, 1H), 8.14 (d, 1H), 8.81 (m, 1H).

15

EXAMPLE 87

N-[2-(2,5-Dimethoxyphenyl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea

39% yield.

20       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 1.18 (b, 6H), 1.55 (b, 2H), 3.09 (c, 1H), 3.27 (m, 1H), 3.37 (s, 3H), 3.49 (p, 1H), 3.72 (s, 3H), 3.9 (s, 3H), 4.45 (b, 1H), 5.98 (b, 1H), 6.51 (d, 1H), 6.55-6.63 (c, 2H), 7.31 (q, 1H), 7.48 (d, 1H), 8.09 (d, 1H), 8.17 (d, 1H), 8.77 (q, 1H).

EXAMPLE 88

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-dimethoxyphenyl)heptyl]urea

25       45% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.2 (b, 6H), 1.44-1.68 (c, 2H), 2.33 (s, 3H), 2.44 (s, 3H), 2.47 (s, 3H), 2.65 (c, 1H), 3.11 (m, 1H), 3.58 (p, 1H), 3.74 (s, 6H), 4.22 (b, 1H), 5.34 (s, 1H), 6.24 (s and c, 3H), 6.54 (s, 1H).

EXAMPLE 89

30       N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethoxyphenyl)octyl]urea  
50% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 3H), 1.2 (b, 8H), 1.64 (b, 2H), 2.33 (s, 3H), 2.45 (s, 3H), 2.5 (s, 3H), 3.15 (c, 1H), 3.27-3.5 (c, 2H), 3.61 (s, 3H), 3.73 (s, 3H), 4.43 (b, 1H), 5.47 (b, 1H), 6.57 (s, 1H), 6.6-6.71 (c, 3H).

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EXAMPLE 90

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-2-[2-(3-methylphenyl)-6,6,6-trifluorohexyl]urea

34% yield.

5        <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.42 (c, 2H), 1.55-1.82 (c, 2H), 2.0 (c, 2H), 2.28 (s, 3H), 2.34 (s, 3H), 2.47 (s, 3H), 2.48 (s, 3H), 2.68 (c, 1H), 3.17 (m, 1H), 3.56 (p, 1H), 4.28 (b, 1H), 5.39 (s, 1H), 6.56 (s, 1H), 6.88 (d) and 6.89 (s) (total 2H), 6.98 (d, 1H), 7.12 (t, 1H).

EXAMPLE 91

10        N-[2-(3-Methylphenyl)heptyl]-N'-(6-pentylthioquinolin-5-yl)urea

53% yield.

15        <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H), 0.9 (t, 3H), 1.04-1.7 (c, 14H), 2.2 (s, 3H), 2.59 (c, 1H), 2.93 (t, 2H), 3.14 (m, 1H), 3.59 (p, 1H), 4.15 (b, 1H), 6.11 (s, 1H), 6.69 (d) and 6.71 (s) (total 2H), 6.89 (d, 1H), 6.99 (t, 1H), 7.33 (q, 1H), 7.62 (d, 1H), 7.98 (d, 1H), 8.13 (d, 1H), 8.82 (q, 1H).

EXAMPLE 92

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(5-chlorobenzo[b]thiophen-3-yl)heptyl]urea

36% yield.

20        <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.22 (b, 6H), 1.63 (b, 2H), 2.23 (s, 3H), 2.4 (s, 3H), 2.46 (s, 3H), 3.21 (m, 1H), 3.51 (c, 2H), 4.32 (b, 1H), 5.44 (b, 1H), 6.48 (s, 1H), 7.13 (s, 1H), 7.29 (c, 1H), 7.72 (d, 1H), 7.41 (s, 1H).

EXAMPLE 93

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-dimethylphenyl)heptyl]urea

25        34% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.21 (b, 6H), 1.57 (b, 2H), 2.23 (s, 6H), 2.33 (s, 3H), 2.46 (s, 3H), 2.48 (s, 3H), 2.61 (c, 1H), 3.13 (m, 1H), 3.56 (p, 1H), 4.21 (b, 1H), 5.33 (s, 1H), 6.55 (s, 1H), 6.67 (s, 2H), 6.78 (s, 1H).

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EXAMPLE 94N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)octyl]urea

35% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.84 (t, 3H), 1.19 (b, 8H), 1.6 (b, 2H), 2.18 (s, 3H),  
5 2.23 (s, 3H), 2.31 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.04 (c, 1H), 3.2 (m, 1H), 3.52 (p,  
1H), 4.22 (b, 1H), 5.37 (b, 1H), 6.54 (s, 1H), 6.84 (d) and 6.85 (s), (total 2H), 6.92 (d,  
1H).

EXAMPLE 95

10 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-2-{3-  
methylphenyl}hexyl]urea

44% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79, 0.8, 0.81, 0.82 (2d, 6H), 0.92-1.18 (c, 2H),  
1.38-1.74 (c, 3H), 2.28 (s, 3H), 2.33 (s, 3H), 2.46 (s, 3H), 2.48 (s, 3H), 2.63 (c, 1H), 3.14  
(m, 1H), 3.58 (p, 1H), 4.22 (b, 1H), 5.36 (s, 1H), 6.55 (s, 1H), 6.87 (d) and 6.88 (s) (total  
15 2H), 6.96 (d, 1H), 7.09 (t, 1H).

EXAMPLE 96

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-{2,5-dimethylphenyl}-4-  
phenylbutyl]urea

33% yield.

20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.8-1.96 (m, 1H), 1.99-2.14 (m) and 2.11 (s) (total  
4H), 2.24 (s, 3H), 2.3 (s, 3H), 2.4-2.54 (m, 8H) including 2.44 (s, 3H) and 2.49 (s, 3H),  
3.08 (c, 1H), 3.3 (m, 1H), 3.49 (p, 1H), 4.25 (b, 1H), 5.37 (s, 1H), 6.54 (s, 1H), 6.87 (d)  
and (6.9 (s) (total 2H), 6.95 (d, 1H), 7.08 (d) and 7.09 (s) (total 2H), 7.14 (m, 1H), 7.23  
(m, 2H).

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EXAMPLE 97

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-5-  
phenylpentyl]urea

19% yield.

30 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.4-1.8 (c, 4H), 2.17 (s, 3H), 2.22 (s, 3H), 2.3 (s,  
3H), 2.43 (s, 3H), 2.48 (s, 3H), 2.53 (c, 2H), 3.08 (c, 1H), 3.2 (m, 1H), 3.52 (p, 1H), 4.22  
(b, 1H), 5.36 (s, 1H), 6.52 (s, 1H), 6.81 (s) and 6.83 (d) (total 2H), 6.91 (d, 1H), 7.08 (d,  
2H), 7.13 (m, 1H), 7.23 (m, 2H).



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EXAMPLE 98N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)-6-methylheptyl]urea

59% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76 (t, 6H), 1.06-1.34 (c, m, 4H), 1.43 (h, 1H), 1.75 (c, 2H), 2.13 (s, 3H), 2.37 (s, 3H), 2.43 (s, 3H), 3.48 (m, 1H), 3.56-3.82 (c, 2H), 4.21 (c, 1H), 5.28 (s, 1H), 6.37 (s, 1H), 7.28 (m, 1H), 7.36 (t, 1H), 7.46 (m, 2H), 7.67 (d, 1H), 7.83 (m, 1H), 8.13 (m, 1H).

EXAMPLE 99N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)-6-methylheptyl]urea

31% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.74, 0.76, 0.79 (2d, 6H), 1.06-1.32 (m, c, 10H), 1.42 (h, 1H), 1.78 (c, 2H), 2.42 (s, 3H), 2.68 (q, 2H), 3.02 (q, 2H), 3.53 (m, 2H), 3.72 (c, 1H), 4.20 (c, 1H), 5.27 (s, 1H), 6.42 (s, 1H), 7.28 (m, 1H), 7.34 (t, 1H), 7.46 (m, 2H), 7.67 (d, 1H), 7.81 (m, 1H), 8.12 (m, 1H).

EXAMPLE 100N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-6-methylheptyl]urea

38% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77, 0.79, 0.81 (2d, 6H), 1.04-1.72 [c, m including 2t (1.29, 1.31, 6H), total 13H], 2.18 (s, 3H), 2.22 (s, 3H), 2.46 (s, 3H), 2.81 (q, 2H), 2.98-3.25 [m including q (3.08, 2H), total 4H], 3.53 (p, 1H), 4.2 (c, 1H), 5.32 (s, 1H), 6.56 (s, 1H), 6.84 (d, 1H), 6.92 (d, 1H), 7.26 (s, 1H).

EXAMPLE 101N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)heptyl]urea

15% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79 (t, 3H), 1.23 (m, c, 12H), 1.65-1.94 (c, 2H), 2.42 (s, 3H), 2.68 (q, 2H), 3.02 (q, 2H), 3.54 (c, 2H), 3.72 (c, 1H), 4.22 (c, 1H), 5.28 (s, 1H), 6.42 (s, 1H), 7.32 (m, 2H), 7.45 (m, 2H), 7.67 (d, 1H), 7.82 (m, 1H), 8.11 (m, 1H).

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EXAMPLE 102

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-6-phenylhexyl]urea

57% yield.

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.14-1.36 [c including 2t (1.28, 1.3, 6H), total 10H], 1.48-1.8 (m, c, 4H), 2.17 (s, 3H), 2.23 (s, 3H), 2.46 (s, 3H), 2.52 (t, 2H), 2.81 (q, 2H), 2.29-3.13 [c and q (3.07, 2H) total 3H], 3.2 (m, 1H), 3.52 (p, 1H), 4.21 (c, 1H), 5.33 (s, 1H), 6.56 (s, 1H), 6.85 (d, 1H), 6.93 (d, 1H), 7.13 (m, 3H), 7.24 (m, 3H).

EXAMPLE 103

10 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)heptyl]urea  
48% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.2 (c, 6H), 1.29, 1.31 (2t, 6H), 1.47-1.72 (c, 2H), 2.17 (s, 3H), 2.23 (s, 3H), 2.46 (s, 3H), 2.82 (q, 2H), 2.98-3.13 [c including q (3.08), total 3H], 3.19 (m, 1H), 3.53 (p, 1H), 4.18 (b, 1H), 5.29 (s, 1H), 6.56 (s, 1H),  
15 6.84 (d) and 6.85 (s), total 2H, 6.92 (d, 1H).

EXAMPLE 104

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,4,6-trimethylphenyl)octyl]urea  
27% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 3H), 1.2 (c, 8H), 1.7 (c, 2H), 2.16 (s, 3H),  
20 2.22 (s, 3H), 2.28 (s, 3H), 2.3 (s, 3H), 2.42 (s, 3H), 2.48 (s, 3H), 3.28 (c, 2H), 3.68 (m, 1H), 4.14 (b, 1H), 5.29 (s, 1H), 6.48 (s, 1H), 6.66 (s, 1H), 6.69 (s, 1H).

EXAMPLE 105

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-6,6,6-trifluorohexyl]urea

25 20% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.29, 1.32 (2t, 6H), 1.43 (c, 2H), 1.63 (c, 1H), 1.78 (c, 1H), 2.0 (c, 2H), 2.2 (s, 3H), 2.24 (s, 3H), 2.46 (s, 3H), 2.84 (q, 2H), 3.0-3.15 [c including t (3.09) total 3H], 3.22 (m, 1H), 3.49 (p, 1H), 4.25 (b, 1H), 5.34 (s, 1H), 6.58 (s, 1H), 6.86 (d, 2H), 6.95 (d, 1H).

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EXAMPLE 106

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(5-methylbenzo[b]thiophen-3-yl)heptyl]urea

10% yield.

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (c, 3H), 1.24 (c, 6H), 1.74 (c, 2H), 2.2 (s, 3H), 2.4 (s, 3H), 2.46 (s, 6H), 3.25 (m, 1H), 3.5 (t, 2H), 4.28 (b, 1H), 5.37 (s, 1H), 6.45 (s, 1H), 6.99 (s, 1H), 7.15 (d, 1H), 7.55 (s, 1H), 7.71 (d, 1H).

EXAMPLE 107

10 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2-chlorobenzo[b]thiophen-3-yl)heptyl]urea

32% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79 (c, 3H), 1.2 (c, 6H), 1.79 (c, 1H), 1.91 (c, 1H), 2.23 (s, 3H), 2.37 (s, 3H), 2.46 (s, 3H), 3.4-3.59 (c, 2H), 3.79 (c, 1H), 4.27 (b, 1H), 5.36 (s, 1H), 6.47 (s, 1H), 7.3 (m, 2H), 7.67 (m, 1H), 7.76 (c, 1H).

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EXAMPLE 108

N-[2-(2,5-Dimethylphenyl)heptyl]-N'-[6-methylthioquinolin-5-yl]urea

33% yield.

20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.16 (c, 6H), 1.5 (c, 2H), 2.0 (s, 3H), 2.13 (s, 3H), 2.47 (s, 3H), 2.96 (m, 1H), 3.16 (m, 1H), 3.55 (p, 1H), 4.09 (b, 1H), 5.97 (s, 1H), 6.7 (s, 1H), 6.77 (q, 2H), 7.34 (q, 1H), 7.56 (d, 1H), 8.03 (d, 1H), 8.2 (d, 1H), 8.82 (q, 1H).

EXAMPLE 109

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-6-methylheptyl]urea

25

35% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77, 0.79, 0.81 (2d, 6H), 1.04-1.7 (c, 7H), 2.18 (s, 3H), 2.23 (s, 3H), 2.31 (s, 3H), 2.44 (s, 3H), 2.48 (s, 3H), 3.04 (c, 1H), 3.19 (m, 1H), 3.53 (p, 1H), 4.2 (b, 1H), 5.33 (s, 1H), 6.53 (s, 1H), 6.84 (d and s, 2H), 6.92 (d, 1H).

EXAMPLE 110

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-5-phenylpentyl]urea

37% yield.

- 5       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.26, 1.29, 1.31, 1.33 (2t, 6H), 1.41-1.82 (c, 4H), 2.17 (s, 3H), 2.22 (s, 3H), 2.46 (s, 3H), 2.54 (c, 2H), 2.81 (q, 2H), 3.0-3.24 [c and including q (3.08), total 4H], 3.52 (p, 1H), 4.2 (b, 1H), 5.31 (s, 1H), 6.56 (s, 1H), 6.82, 6.85 (s and d, 2H), 6.91 (d, 1H), 7.08 (d, 2H), 7.15 (d, 1H), 7.23 (t, 2H).

EXAMPLE 111

- 10       N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)octyl]urea  
26% yield.

- <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 3H), 1.19 (c, 8H), 1.27, 1.29, 1.32, 1.34 (2t, 6H), 1.54 (c, 1H), 1.67 (c, 1H), 2.18 (s, 3H), 2.23 (s, 3H), 2.46 (s, 3H), 2.82 (q, 2H), 2.98-3.14 [c including t (3.08) total 3H], 3.19 (m, 1H), 3.53 (p, 1H), 4.2 (b, 1H), 5.31 (s, 1H), 6.56 (s, 1H), 6.83, 6.85 (s and d, 2H), 6.92 (d, 1H).

EXAMPLE 112

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-5-methylhexyl]urea

39% yield.

- 20       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79, 0.80, 0.81, 0.82 (2d, 6H), 0.92-1.18 (c, 2H), 1.27, 1.29, 1.31, 1.34 (2t, 6H), 1.4-1.75 (c, 3H), 2.17 (s, 3H), 2.23 (s, 3H), 2.46 (s, 3H), 2.82 (q, 2H), 2.93-3.13 [c including t (3.08), total 3H], 3.2 (m, 1H), 3.53 (p, 1H), 4.2 (b, 1H), 5.3 (s, 1H), 6.56 (s, 1H), 6.83, 6.85 (d and s, 2H), 6.92 (d, 1H).

EXAMPLE 113

- 25       N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2-chlorobenzo[b]thiophen-3-yl)-6-methylheptyl]urea

19% yield.

- <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.73, 0.75, 0.76, 0.78 (2d, 6H), 1.01-1.42 [c and 2t (1.22, 1.23, 1.24, 1.25, 1.27, 1.28), total 10H], 1.41 (h, 1H), 1.79 (c, 1H), 1.92 (c, 1H), 2.44 (s, 3H), 2.74 (c, 2H), 3.02 (q, 2H), 3.48 (c, 2H), 3.8 (c, 1H), 4.26 (b, 1H), 5.3 (s, 1H), 6.5 (s, 1H), 7.29 (m, 2H), 7.66 (m, 1H), 7.77 (c, 1H).

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EXAMPLE 114

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2-chlorobenzo[b]thiophen-3-yl)-5-methylhexyl]urea

35% yield.

5  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.75-1.3 [c including 2d (0.77, 0.78, 0.79, 0.80, 6H), and 2t (1.22, 1.23, 1.24, 1.25, 1.27, 1.28, 6H), total 14H], 1.47 (h, 1H), 1.75-1.2 (c, 2H), 2.44 (s, 3H), 2.75 (c, 2H), 3.02 (q, 2H), 3.46 (c, 2H), 3.8 (c, 1H), 4.27 (b, 1H), 5.3 (s, 1H), 6.5 (s, 1H), 7.3 (m, 2H), 7.66 (m, 1H), 7.77 (c, 1H).

EXAMPLE 115

10 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(5,6,7,8-tetrahydronaphth-1-yl)heptyl]urea

36% yield.

15  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.82 (t, 3H), 1.2 (c, 6H), 1.29, 1.31, 1.34 (2t, 6H), 1.45-1.82 (c, 6H), 2.46 (s, 3H), 2.7 (c, 4H), 2.83 (q, 2H), 3.03-3.28 (c including q (3.08), total 4H), 3.46 (p, 1H), 4.23 (b, 1H), 5.3 (s, 1H), 6.58 (s, 1H), 6.85, 6.88, 6.91 (2d, 2H), 6.98 (t, 1H).

EXAMPLE 116

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-dimethylphenyl)heptyl]urea

20% yield.

20  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.82 (t, 3H), 1.21 (c, 6H), 1.28, 1.30, 1.32, 1.35 (2t, 6H), 1.6 (c, 2H), 2.33 (s, 6H), 2.45 (s, 3H), 2.61 (c, 1H), 2.84 (q, 2H), 3.05-3.2 [c and q (3.1), total 3H], 3.56 (p, 1H), 4.2 (b, 1H), 5.3 (s, 1H), 6.59 (s, 1H), 6.67 (s, 2H), 6.78 (s, 1H).

EXAMPLE 117

25 N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2-chlorobenzo[b]thiophen-3-yl)heptyl]urea

51% yield.

30  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.79 (t, 3H), 1.04-1.32 [c including 2t (1.22, 1.23, 1.24, 1.25, 1.27, 1.28), total 12H], 1.81, (c, 1H), 1.94 (c, 1H), 2.44 (s, 3H), 2.76 (c, 2H), 3.02 (q, 2H), 3.48 (c, 2H), 3.8 (c, 1H), 4.27 (b, 1H), 5.3 (s, 1H), 6.5 (s, 1H), 7.3 (m, 2H), 7.66 (m, 1H), 7.78 (c, 1H).

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EXAMPLE 118N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-dimethylphenyl)octyl]urea

19% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83 (t, 3H), 1.2 (c, 8H), 1.27, 1.30, 1.32, 1.35 (2t, 6H), 1.45-1.72 (c, 2H), 2.22 (s, 6H), 2.45 (s, 3H), 2.6 (c, 1H), 2.84 (q, 2H), 3.05-3.2 [c and q (3.1), total 3H], 3.56 (h, 1H), 4.23 (b, 1H), 5.35 (s, 1H), 6.58 (s, 1H), 6.67 (s, 2H), 6.77 (s, 1H).

EXAMPLE 119

N-[2,4-Bis(ethylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethyl-4-methoxyphenyl)heptyl]urea

50% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.2 (c, 6H), 1.26, 1.29, 1.31, 1.34 (2t, 6H), 1.44-1.72 (c, 2H), 2.09 (s, 3H), 2.18 (s, 3H), 2.46 (s, 3H), 2.82 (q, 2H), 2.96 (c, 1H), 3.01-3.2 [c including q (3.07), total 3H], 3.48 (p, 1H), 3.78 (s, 3H), 4.18 (b, 1H), 5.29 (s, 1H), 6.48 (s, 1H), 6.56 (s, 1H), 6.77 (s, 1H).

EXAMPLE 120

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(5-methylbenzo[b]thiophen-3-yl)heptyl]urea

10% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82 (t, 3H), 1.23 (c, 6H), 1.73 (c, 2H), 2.2 (s, 3H), 2.41 (s, 3H), 2.46 (s, 6H), 3.25 (p, 1H), 3.5 (t, 2H), 4.28 (b, 1H), 5.35 (s, 1H), 6.45 (s, 1H), 6.99 (s, 1H), 7.15 (d, 1H), 7.55 (s, 1H), 7.7 (d, 1H).

EXAMPLE 121

N-[2-(2-Chlorobenzo[b]thiophen-3-yl)-5-methylhexyl]-N'-(2,6-diisopropylphenyl)urea

43% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.72-1.31 (c, 20H), 1.46 (h, 1H), 1.78 (c, 1H), 1.82 (c, 1H), 3.06 (c, 2H), 3.44 (c, 2H), 3.76 (c, 1H), 4.01 (b, 1H), 5.52 (s, 1H), 7.06 (c, 2H), 7.26 (c, 3H), 7.64 (c, 1H), 7.71 (c, 1H).

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EXAMPLE 122

N-(2,6-Diisopropylphenyl)-N'-[2-(5-methylbenzo[b]thiophen-3-yl)-5-methylhexyl]urea

44% yield.

5       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76-1.3 [m, c including d (0.79, 0.81), total 21H], 1.46 (h, 1H), 1.68 (c, 2H), 2.45 (s, 3H), 3.08 (c) and 3.17 (m), (total 2H), 3.47 (c, 2H), 4.08 (b, 1H), 5.57 (s, 1H), 6.86 (s, 1H), 7.05 (s, 1H), 7.07 (s, 1H), 7.14 (d, 1H), 7.22 (d, 1H), 7.51 (s, 1H), 7.67 (d, 1H).

EXAMPLE 123

10       N-[2-(Benzo[b]thiophen-3-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea

41% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76-1.31 (c, 20H), 1.68 (c, 2H), 1.95 (c, 1H), 3.05 (c, 2H), 3.25 (p, 1H), 3.49 (c, 2H), 4.1 (b, 1H), 5.72 (s, 1H), 6.92 (s, 1H), 7.06 (s, 1H), 7.08 (s, 1H), 7.21-7.38 (c, 3H), 7.74 (m, 1H), 7.8 (m, 1H).

EXAMPLE 124

15       N-[2-(Benzo[b]thiophen-3-yl)-6-methylheptyl]-N'-(2,6-diisopropylphenyl)urea

58% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.74-1.48 [m, c including 2d (0.76, 0.77, 0.78, 0.80) total 22H], 1.67 (m, 2H), 1.8 (c, 1H), 3.07 (c, 2H), 3.25 (p, 1H), 3.48 (c, 2H), 4.1 (b, 1H),  
20       5.68 (s, 1H), 6.92 (s, 1H), 7.06 (s, 1H), 7.08 (s, 1H), 7.2-7.4 (c, 3H), 7.74 (m, 1H), 7.8 (m, 1H).

EXAMPLE 125

N-[2-(2-Chlorobenzo[b]thiophen-3-yl)-6-methylheptyl]-N'-(2,6-diisopropylphenyl)urea

25       70% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.7-1.3 [c and 2d (0.73, 0.75, 0.76, 0.78), total 22H], 1.4 (h, 1H), 1.73 (c, 1H), 1.91 (c, 1H), 3.06 (c, 2H), 3.44 (c, 2H), 3.76 (c, 1H), 4.02 (b, 1H), 5.54 (s, 1H), 7.06 (c, 2H), 7.2-7.32 (c, 3H), 7.64 (m, 1H), 7.71 (c, 1H).

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EXAMPLE 126

N-(2,6-Diisopropylphenyl)-N'-[2-(5-methylbenzo[b]thiophen-3-yl)-6,6,6-trifluorohexyl]urea

70% yield.

- 5     <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.8-1.3 (c, 12H), 1.51 (m, 2H), 1.78 (m, 2H), 2.0 (m, 2H), 2.46 (s, 3H), 3.07 (c, 2H), 3.25 (p, 1H), 3.48 (m, 2H), 4.11 (b, 1H), 5.6 (s, 1H), 6.92 (s, 1H), 7.07 (d, 2H), 7.16 (d, 1H), 7.24 (d, 1H), 7.52 (s, 1H), 7.69 (d, 1H).

EXAMPLE 127

- 10     N-[2-(2-Chlorobenzo[b]thiophen-3-yl)-6,6,6-trifluorohexyl]-N'-(2,6-diisopropylphenyl)urea

46% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-1.27 (c, 12H), 1.42 (c, 2H), 1.85 (c, 1H), 2.02 (c, 3H), 3.08 (c, 2H), 3.47 (c, 2H), 3.79 (c, 1H), 4.08 (b, 1H), 5.58 (s, 1H), 7.07 (d, 2H), 7.2-7.35 (c, 3H), 7.7 (c, 2H).

15

EXAMPLE 128

N-(2,6-Diisopropylphenyl)-N'-[2-(naphth-2-yl)-6,6,6-trifluorohexyl]urea

67% yield.

- 20     <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.63-1.14 (c, 12H), 1.45 (m, 2H), 1.68-2.08 (c, 4H), 2.9 (c, 1H), 3.09 (c, 1H), 3.4 (c, 1H), 3.6 (c, 1H), 3.79 (c, 1H), 4.07 (b, 1H), 5.67 (s, 1H), 7.02 (d, 2H), 7.2 (m, 2H), 7.34 (t, 1H), 7.47 (m, 2H), 7.68 (d, 1H), 7.82 (m, 1H), 8.06 (c, 1H).

EXAMPLE 129

N-[7,7-Difluoro-2-(naphth-1-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea

58% yield.

- 25     <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.63-1.46 (c, 16H), 1.57-1.9 (c, 4H), 2.92 (c, 1H), 3.08 (c, 1H), 3.39 (m, 1H), 3.59 (c, 1H), 3.75 (c, 1H), 4.03 (b, 1H), 5.57 (s, 1H), 5.48, 5.67, 5.86 (3t, total 1H), 7.0 (d, 1H), 7.18 (t, 2H), 7.32 (t, 1H), 7.44 (m, 2H), 7.65 (d, 1H), 7.8 (m, 1H), 8.05 (m, 1H).



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EXAMPLE 130

N-[7,7-difluoro-2-(2-chlorobenzo[b]thiophen-3-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea

73% yield.

5       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.73-1.5 (c, 16H), 1.56-1.85 (c, 3H), 1.96 (c, 1H), 3.07 (c, 2H), 3.47 (c, 2H), 3.77 (c, 1H), 4.05 (b, 1H), 5.59 (s, 1H), 5.50, 5.69, 5.88 (3t, total 1H), 7.06 (d, 2H), 7.2-7.35 (c, 3H), 7.62-7.77 (c, 2H).

EXAMPLE 131

N-[2-(5-Chlorobenzo[b]thiophen-3-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea

10       59% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-1.46 (c, 21H), 1.65 (m, 2H), 3.01-3.24 (m, 3H), 3.46 (m, 2H), 4.04 (b, 1H), 5.6 (s, 1H), 7.02 (s, 1H), 7.08 (c, 2H), 7.26 (m, 2H), 7.71 (m, 2H).

EXAMPLE 132

15       N-[2-(2-Chlorobenzo[b]thiophen-3-yl)heptyl]-N'-(2,6-diisopropylphenyl)urea

60% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.74-1.42 (c, 21H), 1.75 (c, 1H), 1.92 (c, 1H), 3.07 (c, 2H), 3.45 (c, 2H), 3.76 (c, 1H), 4.02 (b, 1H), 5.74 (s, 1H), 7.06 (c, 2H), 7.2-7.34 (m, 3H), 7.65 (m, 1H), 7.7 (c, 1H).

20

EXAMPLE 133

N-[2-(5-Chlorobenzo[b]thiophen-3-yl)-6,6,6-trifluorohexyl]-N'-(2,6-diisopropylphenyl)urea

72% yield.

25       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.82-1.32 (c, 12H), 1.5 (m, 2H), 1.76 (c, 2H), 2.0 (c, 2H), 3.07 (c, 2H), 3.23 (p, 1H), 3.48 (c, 2H), 4.11 (b, 1H), 5.68 (s, 1H), 7.07, 7.09 (d and s, 3H), 7.21-7.34 (m, 2H), 7.72, 7.75 (d and s, 2H).

EXAMPLE 134

N-(2,6-(Diisopropylphenyl))-N'-[2-(5-methylbenzo[b]thiophen-3-yl)heptyl]urea

50% yield.

30       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76-1.32 (c, 21H), 1.67 (c, 2H), 2.45 (s, 3H), 3.08 (c, 2H), 3.2 (p, 1H), 3.47 (t, 2H), 4.06 (b, 1H), 5.6 (s, 1H), 6.86 (s, 1H), 7.07 (d, 2H), 7.14 (d, 1H), 7.22 (d, 1H), 7.52 (s, 1H), 7.67 (d, 1H).

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EXAMPLE 135

N-[2-(5-Chlorobenzof[b]thiophen-3-yl)-6-methylheptyl]-N'-(2,6-diisopropylphenyl)urea

49% yield.

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.75-1.8 [c including 2d (0.76, 0.78, 0.79, 0.80), total 23H], 2.26 (m, 2H), 3.07 (p, 2H), 3.18 (p, 1H), 3.47 (c, 2H), 4.06 (b, 1H), 5.65 (s, 1H), 7.03 (s, 1H), 7.08 (c, 2H), 7.2-7.3 (m, 2H), 7.71 (m, 2H).

EXAMPLE 136

N-(2,6-Diisopropylphenyl)-N'-[2-(2,5-dimethylphenyl)-6,6,6-trifluorohexyl]urea

10 37% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.9-1.76 (c, 16H), 1.98 (m, 2H), 2.08 (s, 3H), 2.19 (s, 3H), 2.95-3.21 (c, 4H), 3.52 (p, 1H), 3.97 (b, 1H), 5.6 (b, 1H), 6.74 (s, 1H), 6.83 (d, 1H), 6.9 (d, 1H), 7.11 (d, 2H), 7.28 (t, 1H).

EXAMPLE 137

15 N-[7,7-Difluoro-2-(2,5-dimethylphenyl)heptyl]-N'-(2,6-diisopropylphenyl)urea

65% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.92-1.82 (c, 20H), 2.06 (s, 3H), 2.18 (s, 3H), 2.98 (c, 1H), 3.12 (c, 3H), 3.51 (p, 1H), 3.95 (b, 1H), 5.61 (s, 1H), 5.52, 5.71, 5.9 (3t, total 1H), 6.74 (s, 1H), 6.81 (d, 1H), 6.89 (d, 1H), 7.1 (d, 2H), 7.27 (t, 1H).

20

EXAMPLE 138

N-(2,6-Diisopropylphenyl)-N'-[2-(naph-1-yl)heptyl]urea

61% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78 (t, 3H), 0.9-1.3 (m and c, 18H), 1.72 (c, 2H), 2.85-3.16 (c, 2H), 3.41 (m, 1H), 3.58 (c, 1H), 3.72 (c, 1H), 4.02 (b, 1H), 5.49 (s, 1H), 7.01 (d, 2H),  
25 7.18 (m, 2H), 7.31 (t, 1H), 7.44 (m, 2H), 7.65 (d, 1H), 7.8 (m, 1H), 8.07 (m, 1H).

EXAMPLE 139

N-(2,6-Diisopropylphenyl)-N'-[6-methyl-2-(naph-1-yl)heptyl]urea

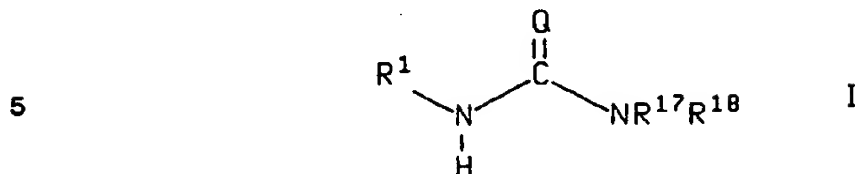
59% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.74 (t, 6H), 0.91-1.29 (m and c, 18H), 1.4 (h, 1H), 1.7 (c, 2H), 2.84-3.16 (c, 2H), 3.41 (m, 1H), 3.51-3.8 (c, 2H), 4.02 (c, 1H), 5.51 (s, 1H), 7.0 (d, 2H),  
30 7.19 (m, 2H), 7.31 (t, 1H), 7.44 (m, 2H), 7.66 (d, 1H), 8.07 (m, 1H).

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CLAIMS

1. A compound of the formula



wherein Q is oxygen or sulfur

$\text{R}^{17}$  is  $-(\text{CH}_2)_n-(\text{CR}^{19}\text{R}^{20})_z(\text{CH}_2)_r-\text{Ar}$  XXXVIII

10 wherein n is 0 or an integer from 1 to 3;

z is 0 or 1;

and r is 0 or an integer from 1 to 4;

$\text{R}^{19}$  and  $\text{R}^{20}$  are independently selected from hydrogen, optionally halogenated  
 (C<sub>1</sub>-C<sub>12</sub>) alkyl, optionally substituted aryl-(C<sub>1</sub>-C<sub>5</sub>) alkyl, (C<sub>3</sub>-C<sub>8</sub>) cycloalkyl-(C<sub>1</sub>-C<sub>5</sub>) alkyl and  
 15 Ar; or  $\text{R}^{19}$  and  $\text{R}^{20}$  and the carbon to which they are attached form a (C<sub>4</sub>-C<sub>7</sub>) cycloalkyl  
 ring or a benzene-fused (C<sub>5</sub>-C<sub>7</sub>) cycloalkyl or -heteroalkyl ring; with the proviso that  $\text{R}^{19}$   
 and  $\text{R}^{20}$  cannot both be hydrogen;

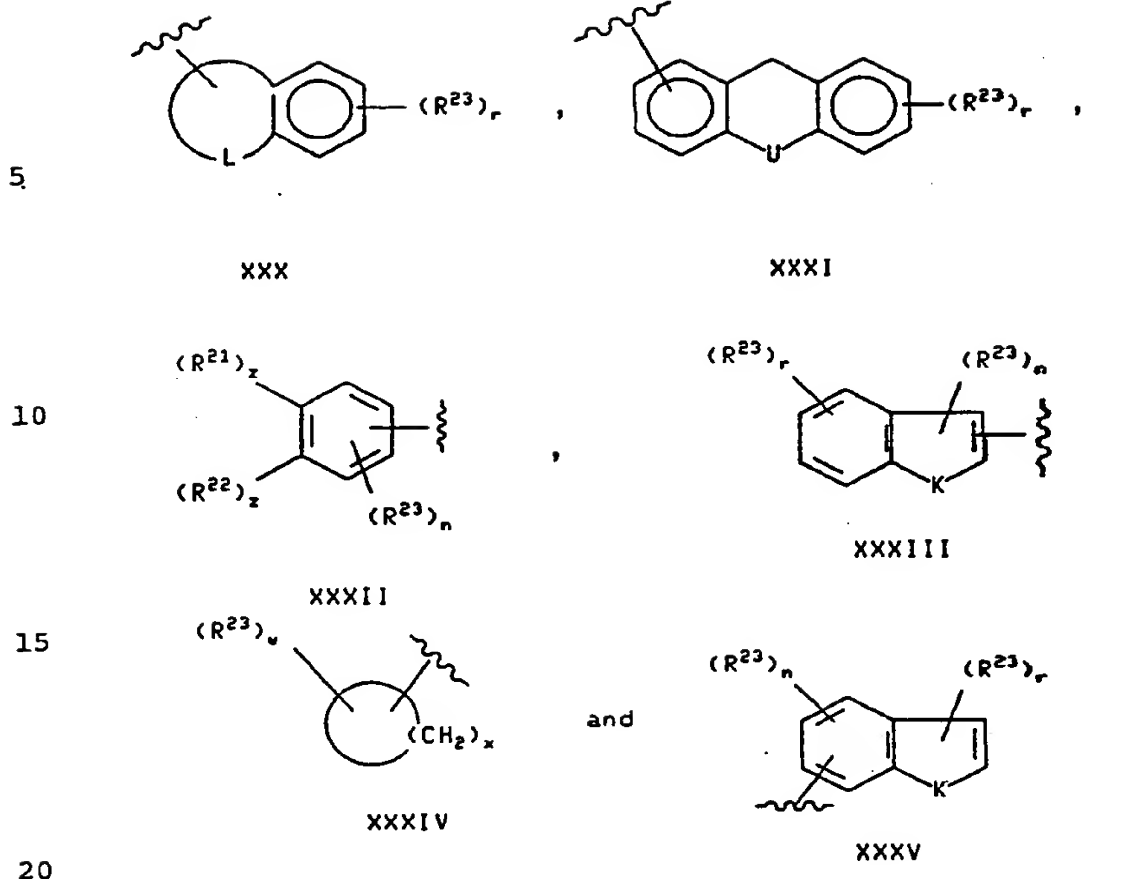
Ar is selected from the group consisting of

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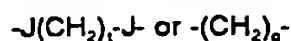


wherein U is J, a direct bond -CH=CH- or -CH<sub>2</sub>CH<sub>2</sub>-;

25 z, n and r are as defined above; x is an integer from 3 to 10 and w is 0 or an integer from 1 to x-1.

R<sup>21</sup>, R<sup>22</sup> and each R<sup>23</sup> is independently selected from the group consisting of optionally halogenated (C<sub>1</sub>-C<sub>6</sub>)alkyl, optionally halogenated (C<sub>1</sub>-C<sub>6</sub>)alkoxy, optionally halogenated (C<sub>1</sub>-C<sub>6</sub>)alkylthio, phenyl and halogen; wherein the alkyl groups in said  
30 alkyl, alkoxy and alkylthio groups may be straight chained or if comprising three or more carbons may be branched, cyclic or a combination of cyclic and branched or straight chained moieties;

or R<sup>21</sup> and R<sup>22</sup> together form a group of the formula



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wherein J is oxygen or sulfur;

t is an integer from 1 to 3;

and q is an integer from 3 to 5;

K is J- or -CH=CH-;

5 L is  $-(CH_2)_u$  or  $-(CH_2)_vJ$ ;

wherein J is as defined above;

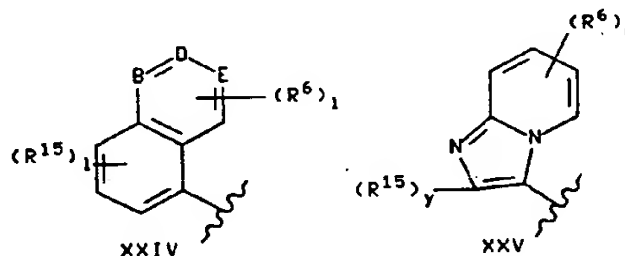
u is an integer 3 to 5;

and v is 2, 3 or 4;

10  $R^{18}$  is hydrogen, optionally substituted  $(C_1-C_6)$ alkyl, optionally substituted  $(C_3-C_8)$ cycloalkyl, or optionally substituted aryl- $(C_1-C_4)$ alkyl; with the proviso that  $R^{18}$  is hydrogen if any one of n, z or r in formula XXXVIII is not 0;

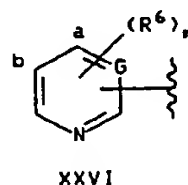
$R^1$  is selected from the group consisting of

15



or

20



25

wherein m is 0 or an integer from 1 to 4;

y is 0 or 1.

Each l is independently selected from 0 to 3;

Each  $R^6$  and  $R^{15}$  is independently selected from the group consisting of halogen,  
 30 optionally halogenated  $(C_1-C_6)$ alkyl, optionally halogenated  $(C_1-C_6)$  alkoxy, optionally halogenated  $(C_1-C_6)$  alkylthio,  $(C_5-C_7)$  cycloalkylthio, phenyl  $(C_1-C_6)$ alkylthio, substituted phenylthio, heteroarylthio, heteroaryloxy,  $(C_1-C_6)$  alkylsulfinyl,  $(C_1-C_6)$  alkylsulfonyl,  $(C_5-C_7)$  cycloalkylsulfinyl,  $(C_5-C_7)$  cycloalkylsulfonyl, phenyl  $(C_1-C_6)$  alkylsulfinyl, phenyl  $(C_1-C_6)$  alkylsulfonyl, substituted phenylsulfinyl, substituted phenylsulfonyl, heteroarylsulfinyl,

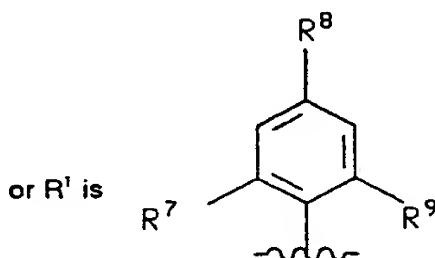
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heteroarylsulfonyl, and  $\text{NR}^{10}\text{R}^{11}$ , wherein  $\text{R}^{10}$  and  $\text{R}^{11}$  are the same or different and are selected from the group consisting of hydrogen,  $(\text{C}_1\text{-C}_6)$  alkyl, phenyl, substituted phenyl,  $(\text{C}_1\text{-C}_6)$  acyl, aroyl, and substituted aroyl, wherein said substituted phenyl and substituted aroyl groups are substituted with one or more substituents independently

5 selected from the group consisting of  $(\text{C}_1\text{-C}_6)$  alkyl,  $(\text{C}_1\text{-C}_6)$  alkoxy,  $(\text{C}_1\text{-C}_6)$  alkylthio, halogen and trifluoromethyl, or  $\text{R}^{10}$  and  $\text{R}^{11}$ , together with the nitrogen to which they are attached, form a piperidine, pyrrolidine or morpholine ring; and

B, D, E and G are selected from the group consisting of nitrogen and carbon, with the proviso that one or more of B, D and E is nitrogen, and with the proviso that

10 when G is nitrogen, the group XVI is attached to the nitrogen of formula I at the 4 or 5 position of the pyrimidine ring (designated by a and b) wherein any of said nitrogens may be oxidized;



XXVII

wherein  $\text{R}^7$ ,  $\text{R}^8$  and  $\text{R}^9$  may be the same or different and each is independently

15 selected from the group consisting of optionally halogenated  $(\text{C}_1\text{-C}_6)$ alkoxy, optionally halogenated  $(\text{C}_1\text{-C}_6)$ alkylthio, optionally halogenated  $(\text{C}_1\text{-C}_6)$ alkyl and halogen; with the proviso that when  $\text{R}^1$  is a group of the formula XXVII Ar is a group of formula XXXIII or XXXV and K is not  $\text{CH}=\text{CH}$  except when  $\text{R}^{19}$  and  $\text{R}^{20}$  are independently selected from hydrogen and halogenated  $(\text{C}_1\text{-C}_{12})$ alkyl with the proviso that  $\text{R}^{19}$  and  $\text{R}^{20}$  are not both

20 hydrogen and r in formula XXXVIII is 0; or a pharmaceutically acceptable salt of said compound.

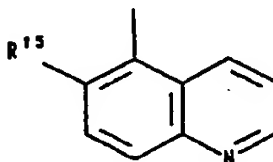
2. The compound according to claim 1 wherein  $\text{R}^1$  is a group of formula XXIV wherein E is carbon and B or D is nitrogen.

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3. The compound according to claim 1 wherein  $R^1$  is a group of formula XXVI wherein G is carbon.

4. The compound according to claim 1 wherein  $R^1$  is a group of formula XXVI wherein G is nitrogen.

5. The compound according to claim 2 wherein  $R^1$  is

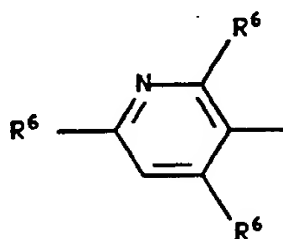


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and  $R^{15}$  is selected from the group consisting of optionally substituted  $(C_1-C_6)$ alkyl and optionally substituted  $(C_1-C_6)$ alkoxy, optionally substituted  $(C_1-C_6)$ alkylthio, preferably alkylthio;  $R^{17}$  is selected from the group consisting of benzenefused  $(C_5-C_8)$  cycloalkyl and optionally substituted  $(C_1-C_6)$ alkyl wherein said substituents are selected from the group consisting of phenyl, benzo[b]thiophenyl, biphenyl, fluorenyl, naphthyl, halogen and  $(C_3-C_{12})$  cycloalkyl wherein said phenyl, naphthyl, cycloalkyl, biphenyl, fluorenyl and benzo[b]thiophenyl groups are optionally substituted with substituents selected from the group consisting of optionally halogenated  $(C_1-C_6)$ alkyl, optionally halogenated  $(C_1-C_6)$ alkoxy, optionally halogenated  $(C_1-C_6)$ alkylthio and halogen and  $R^{18}$  is selected from hydrogen, optionally halogenated  $(C_1-C_6)$ alkyl  $(C_3-C_{12})$ cycloalkyl or optionally substituted aryl- $(C_1-C_6)$ alkyl wherein said aryl groups are optionally substituted with substituents selected from the group consisting of optionally halogenated  $(C_1-C_6)$ alkyl, optionally halogenated  $(C_1-C_6)$ alkoxy, optionally halogenated  $(C_1-C_6)$ alkylthio and halogen.

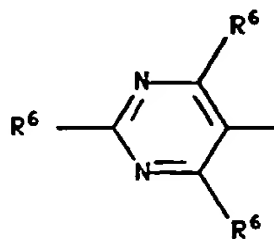
25

6. The compound according to claim 3 or claim 4 wherein  $R^1$  is



XXVIA

or



XXVIB

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and each  $R^5$  is independently selected from the group consisting of  $(C_1-C_6)$ alkyl, and  $(C_1-C_6)$ alkylthio,  $R^{17}$  is selected from the group consisting of benzenefused  $(C_5-C_8)$  cycloalkyl and optionally substituted  $(C_1-C_6)$ alkyl wherein said substituents are selected from the group consisting of phenyl, biphenyl, fluorenyl, benzo[b]thiophenyl, naphthyl, halogen and  $(C_3-C_{12})$  cycloalkyl wherein said phenyl, naphthyl, cycloalkyl, biphenyl, fluorenyl and benzo[b]thiophenyl groups are optionally substituted with substituents selected from the group consisting of optionally halogenated  $(C_1-C_6)$ alkoxy, optionally halogenated  $(C_1-C_6)$ alkyl, optionally halogenated  $(C_1-C_6)$ alkylthio and halogen and  $R^{18}$  is selected from hydrogen, optionally halogenated  $(C_1-C_6)$ alkyl,  $(C_3-C_{12})$ cycloalkyl or optionally substituted aryl- $(C_1-C_6)$ alkyl wherein said aryl groups are optionally substituted with substituents selected from the group consisting of optionally halogenated  $(C_1-C_6)$ alkyl, optionally halogenated  $(C_1-C_6)$ alkoxy, optionally halogenated  $(C_1-C_6)$ alkylthio and halogen with the provisos that if the  $R^1$  is of the formula XXVIA;  $R^6$  in the 6-position is preferably hydrogen or alkyl and each  $R^6$  in the 4- and 2- position is preferably alkylthio and if  $R^1$  is of the formula XXVIB  $R^6$  in the 2-position is preferably hydrogen or alkyl and each  $R^6$  in the 4- and 6-position is preferably alkylthio.

7. A compound according to claim 1, said compound being selected from the group consisting of:

- 20 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(4-isopropylbenzyl)urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2,5-dimethylbenzyl)-N'-(indan-2-yl)urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2,4-dimethylbenzyl)-N'-(indan-2-yl)urea;  
 25 N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(indan-2-yl)-N'-(4-isopropylbenzyl)urea;  
 N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(2,4-dimethylbenzyl)-N'-(indan-2-yl)urea;  
 30 N-(2,5-Dimethylbenzyl)-N-(indan-2-yl)-N'-(6-methylthioquinolin-5-yl)urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2-chlorobenzyl)-N'-(indan-2-yl)urea;  
 N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(2,5-dimethylbenzyl)-N'-(indan-2-yl)urea;



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N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(indan-2-yl)-N'-[4-(3-methylbutyl)benzyl]urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-[4-(3-methylbutyl)benzyl]urea;

5 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(naphth-1-ylmethyl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(naphth-2-ylmethyl)urea;

10 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(4-tert-butylbenzyl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-1-yl)-N'-(4-phenylbenzyl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(naphth-1-ylmethyl)urea;

15 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(naphth-2-ylmethyl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(indan-2-yl)-N'-(2,4,6-trimethylbenzyl)urea;

20 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2,3-dichlorobenzyl)-N'-(indan-2-yl)urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2,2-diphenylethyl]urea;

N-(2,2-Diphenylethyl)-N'-(6-methylthioquinolin-5-yl)urea;

N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-(2,2-diphenylethyl)urea;

N-[4,6-Bis(methylthio)pyrimidin-5-yl]-N'-(2,2-diphenylethyl)urea;

25 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(1-phenylcyclopentyl)methyl]urea;

N-(6-Methylthioquinolin-5-yl)-N'-[(1-phenylcyclopentyl)methyl]urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[{1-(4-methylphenyl)cyclopentyl)methyl]urea;

N-[(1-(4-Methylphenyl)cyclopentyl)methyl]-N'-(6-methylthioquinolin-5-yl)urea;

30 N-(6-Methylthioquinolin-5-yl)-N'-[(1-phenylcyclohexyl)methyl]urea;

N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(1-phenylcyclohexyl)methyl]urea;

N-[(1-(4-Methylphenyl)cyclohexyl)methyl]-N'-(6-methylthioquinolin-5-yl)urea;

N-[4,6-Bis(methylthio)-2-methylpyrimidin-5-yl]-N'-[{1-(4-methylphenyl)cyclohexyl)methyl]urea;

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- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[1-(4-methylphenyl)cyclohexyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-ethyl-2-phenyl)butyl]urea;
- N-[2,4-Bis(isopropylthio)-6-methylpyridin-3-yl]-N'-[(2-ethyl-2-phenyl)butyl]urea;
- 5 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-ethyl-2-(2-methylphenyl))butyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-phenyl-2-propyl)pentyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2-methylphenyl}-2-propyl)pentyl]urea;
- 10 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2-methylphenyl}-2-butyl)hexyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,5-dimethoxyphenyl}-2-propyl)pentyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,3-dimethoxyphenyl}-2-propyl)pentyl]urea;
- 15 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,5-dimethylphenyl}-2-propyl)pentyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2-methylphenyl)hexyl]urea;
- N-[2-(2-Methylphenyl)hexyl]-N'-[6-methylthioquinolin-5-yl]urea;
- 20 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(4-methylphenyl)heptyl]urea;
- N-[2-(4-Methylphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3-methylphenyl)heptyl]urea;
- N-[2-(3-Methylphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;
- N-[2-(3-Methylphenyl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea;
- 25 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)hexyl]urea;
- N-[2-(2,5-Dimethylphenyl)hexyl]-N'-(6-methylthioquinolin-5-yl)urea;
- N-[2-(2,5-Dimethylphenyl)hexyl]-N'-(6-methoxyquinolin-5-yl)urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)heptyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,4-dimethylphenyl)hexyl]urea;
- 30 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3-methylphenyl)hexyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,4-dimethylphenyl)heptyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)heptyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-2-yl)hexyl]urea;
- N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(naphth-1-yl)hexyl]urea;

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- N-(6-Methylthioquinolin-5-yl)-N'-[2-(naphth-1-yl)hexyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,3-dimethoxyphenyl)heptyl]-  
 urea;
- 5 N-[2-(2,3-Dimethoxyphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3-methylphenyl)octyl]urea;  
 N-[2-(3-Methylphenyl)octyl]-N'-(6-methoxyquinolin-5-yl)urea;  
 N-[2-(3-Methylphenyl)octyl]-N'-(6-methylthioquinolin-5-yl)urea;  
 N-[2-(Naphth-1-yl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea;  
 N-[2-(Naphth-1-yl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;
- 10 N-[2-(2,4-Dimethylphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;  
 N-[2-(2,4-Dimethylphenyl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea;  
 N-[2,4-Bis(methyl)-6-methylpyridin-3-yl]-N'-[2-(3,4,5-trimethoxyphenyl)heptyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethyl-4-  
 methoxyphenyl)heptyl]urea;
- 15 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethoxyphenyl)  
 heptyl]urea;  
 N-[2-(2,5-Dimethoxyphenyl)heptyl]-N'-(6-methylthioquinolin-5-yl)urea;  
 N-[2-(2,5-Dimethoxyphenyl)heptyl]-N'-(6-methoxyquinolin-5-yl)urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-  
 20 dimethoxyphenyl)heptyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethoxyphenyl)octyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-2-[2-(3-methylphenyl)-6,6,6-  
 trifluorohexyl]urea;  
 N-[2-(3-Methylphenyl)heptyl]-N'-(6-pentylthioquinolin-5-yl)urea;
- 25 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(5-chlorobenzo[b]thiophen-3-  
 yl)heptyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(3,5-dimethylphenyl)heptyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)octyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-2-{3-  
 30 methylphenyl}hexyl]urea;  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(2-{2,5-dimethylphenyl}-4-  
 phenylbutyl]urea; and  
 N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[2-(2,5-dimethylphenyl)-5-  
 phenylpentyl]urea.

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8. A compound according to claim 1 comprising at least one radiolabel selected from the group consisting of tritium and carbon-14.

9. A pharmaceutical composition comprising an ACAT inhibiting effective amount of a compound according to claim 1 and a pharmaceutically acceptable diluent  
5 or carrier.

10. A method of inhibiting ACAT in a human or animal comprising administering to said human or animal an ACAT inhibiting amount of a compound according to claim 1.

## INTERNATIONAL SEARCH REPORT

PCT/US 93/03539

International Application No

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D213/75; C07D333/62;	C07D239/58; C07D333/54;	C07D215/38; C07C275/28; C07D409/12 A61K31/44
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; C07C ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP,A,0 399 422 (TAKEDA CHEMICAL INDUSTRIES LTD.) 28 November 1990 cited in the application *See definitions of Ar, page 4, lines 43-45 and lines 36-38*	1-6,9
Y	---	1-9
X	EP,A,0 384 320 (WARNER-LAMBERT COMPANY) 29 August 1990 *see definitions of R5*	1,3,4,6,9
Y	---	1-9
X	WO,A,9 113 871 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 19 September 1991 *see definitions of R1 and R3*	1,9
Y	---	1-9
	---	---/---
<p>* Special categories of cited documents:<sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
19 AUGUST 1993		17. 09. 93
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer SCRUTON-EVANS I.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0 477 778 (EISAI CO., LTD.) 1 April 1992 *see definitions of R2 and R15 and R16*	1,3,4,6, 9
Y	---	1-9
P,X	EP,A,0 512 570 (FUJISAWA PHARMACEUTICAL CO., LTD.) 11 November 1992 *see definitions of R1,X ,R2 and specifically example 3(31)*	1,9
P,Y	---	1-9
Y	EP,A,0 439 059 (MITSUBISHI KASEI CORPORATION) 31 July 1991 cited in the application *see whole document*	1-9
Y	---	1-9
Y	EP,A,0 418 071 (PFIZER INC.) 20 March 1991 *see defintions of Q, R1 and R17*	1-9
Y	---	1-9
Y	US,A,4 623 662 (AMERICAN CYANAMID COMPANY) 18 November 1986 cited in the application *see definitions of R1*	1-9
Y	---	1-9
Y	EP,A,0 293 880 (WARNER-LAMBERT COMPANY) 7 December 1988 cited in the application *see defintions of Ar' and Ar*	1-9
P,Y	---	1-9
P,Y	EP,A,0 506 532 (LIPHA, LYONNAISE INDUSTRIELLE PHARMACEUTIQUE) 30 September 1992 *see whole document*	1-9
Y	---	1-9
Y	EP,A,0 447 116 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 18 September 1991 *see definitions of R1 and R3*	1-9

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9303539  
SA 73321

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on  
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0399422	28-11-90	AU-B- 632809	14-01-93
		AU-A- 5518890	29-11-90
		CN-A- 1047859	19-12-90
		CA-A- 2017444	25-11-90
		JP-A- 3261755	21-11-91
EP-A-0384320	29-08-90	CA-A- 2010184	17-08-90
		JP-A- 2258756	19-10-90
		US-A- 4994465	19-02-91
WO-A-9113871	19-09-91	AU-A- 7440691	10-10-91
EP-A-0477778	01-04-92	AU-A- 8469291	02-04-92
		CA-A- 2052191	26-03-92
		CN-A- 1060466	22-04-92
		JP-A- 5092950	16-04-93
EP-A-0512570	11-11-92	AU-A- 1528292	12-11-92
		CN-A- 1067886	13-01-93
		JP-A- 5140102	08-06-93
EP-A-0439059	31-07-91	AU-B- 636946	13-05-93
		AU-A- 6948291	25-07-91
		US-A- 5202351	13-04-93
		JP-A- 4210951	03-08-92
EP-A-0418071	20-03-91	WO-A- 9104027	04-04-91
		CA-A- 2025301	16-03-91
		JP-A- 3120243	22-05-91
US-A-4623662	18-11-86	US-A- 5003106	26-03-91
EP-A-0293880	07-12-88	AU-B- 601846	20-09-90
		AU-A- 1657388	08-12-88
		DE-A- 3873992	01-10-92
		JP-A- 63316761	26-12-88
		US-A- 5015644	14-05-91
EP-A-0506532	30-09-92	FR-A- 2674522	02-10-92
		AU-A- 1309492	01-10-92

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0506532		JP-A- 5097802	20-04-93
		US-A- 5219859	15-06-93
-----			
EP-A-0447116	18-09-91	AU-A- 7276291	12-09-91
		JP-A- 4234839	24-08-92
-----			

EP-0 FORM PCT/93

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